Thrombopoiesis Stimulating Proteins Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
avatrombopag (Doptelet®)[1]	Akarx	Treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment Treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure ▪ Avatrombopag should not be used in an attempt to normalize platelet counts in patients with CLD
eltrombopag (Promacta®)[2]	Novartis	Treatment of thrombocytopenia in adult and pediatric patients ≥ 1 year of age with persistent or chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy ▪ Eltrombopag should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding ▪ Eltrombopag should not be used in an attempt to normalize platelet counts Treatment of thrombocytopenia in patients with chronic hepatitis C (HCV) to allow the initiation and maintenance of interferon-based therapy ▪ Eltrombopag should be used only in patients with chronic HCV whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy ▪ Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic HCV infection ▪ Eltrombopag should not be used in an attempt to normalize platelet counts In combination with standard immunosuppressive therapy for first-line treatment of adult and pediatric patients ≥ 2 years of age with severe aplastic anemia Treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy Eltrombopag is *not* indicated for the treatment of myelodysplastic syndrome (MDS)
fostamatinib disodium hexahydrate (Tavalisse®)[3]	Rigel	Treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment
lusutrombopag (Mulpleta®)[4]	Shionogi	Treatment of thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure ▪ Lusutrombopag should not be used in attempt to normalize platelet counts in patients with CLD

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FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
romiplostim (Nplate®)[5]	Amgen	Treatment of pediatric patients ≥ 1 year of age with ITP for ≥ 6 months who have had an insufficient response to corticosteroids, immune globulins, or splenectomy Treatment of adults with ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy To increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HSARS]) ▪ Romiplostim is not indicated to treat thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than ITP ▪ Romiplostim should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increases their risk for bleeding ▪ Romiplostim should not be used in an attempt to normalize platelet counts

OVERVIEW[6,7]

Platelets are small, circulating cell particles that do not contain nuclei. Platelets are released into the bloodstream by megakaryocytes that reside in the bone marrow. Platelets function to maintain hemostasis by aggregating and forming platelet plugs at sites of injury to limit blood loss.

Thrombocytopenia is generally defined as a platelet count of < 100 × 10^9/L.[8,9] Thrombocytopenia can result in bruising, bleeding, and fatal hemorrhage.[10] Causes of thrombocytopenia include decreased bone marrow production of megakaryocytes, splenic sequestration of platelets, and increased destruction of platelets.

Immune thrombocytopenia (ITP) is an immune-mediated disorder in which platelets are opsonized by autoreactive antibodies and prematurely destroyed by the reticuloendothelial system. In children, ITP is usually an acute, self-limiting disease that often occurs 2 to 3 weeks after a viral infection or immunization. Spontaneous remission in children typically occurs within 2 to 8 weeks. In adults, ITP has an insidious onset with no preceding viral or other illness and typically has a chronic course. Many adult cases of ITP are diagnosed incidentally after a routine complete blood count (CBC). Signs and symptoms of ITP are highly variable and range from asymptomatic with mild bruising or mucosal bleeding to frank hemorrhage from any site. Severity of ITP in adults is dependent on the presence of active bleeding, as well as platelet count, patient age, patient's lifestyle related to risk of bleeding, and presence of additional risk factors for bleeding, such as uremia or chronic liver diseases (CLD).

Primary ITP is defined as an autoimmune disorder with isolated thrombocytopenia (platelet count < 100 × 10^9/L). Other causes or disorders that may result in thrombocytopenia are not present; as such, it is considered a diagnosis of exclusion. There are not specific clinical or laboratory parameters utilized to determine the diagnosis with accuracy. The main clinical concern in primary ITP is the risk for bleeding; however, bleeding symptoms may not always occur. Primary ITP is also defined by the length of time since diagnosis – newly diagnosed (< 3 months), persistent (between 3 and 12 months), and chronic (≥ 12 months). Secondary causes of ITP include drug-induced, autoimmune diseases such as systemic lupus erythematosus (SLE), and viral infections such as human immunodeficiency virus (HIV) and hepatitis C

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(HCV).[11] Severe ITP is defined as clinically relevant if it requires treatment or if there is occurrence of new bleeding symptoms that require additional treatment or increased drug dose to control bleeding.

In 2019, an international consensus report on primary ITP provided a review of updated therapies for the management of ITP in children and adults.[12] Treatment decisions should be individualized depending on the extent of bleeding, platelet count, patient age, presence of fatigue, assessment of risk factors for bleeding, patient preference, and access to care. Corticosteroids (e.g., dexamethasone, methylprednisolone, prednisolone) are recommended as initial treatment in newly-diagnosed adults who require treatment and do not have a relative contraindication to therapy. Intravenous gammaglobulin (IVIG) or intravenous (IV) anti-D may be appropriate in patients with bleeding, at high risk for bleeding, who require a surgical procedure, or who are unresponsive to corticosteroid therapy. The potential triggering of disseminated intravascular coagulation (DIC) or hemolysis as well as Rh(D) blood typing must be considered when using anti-D. Subsequent treatments with robust evidence include rituximab, the thrombopoietin receptor agonists (TPO-RAs) eltrombopag (Promacta), avatrombopag (Doptelet), and romiplostim (Nplate), as well as fostamatinib (Tavalisse). Although not approved for the treatment of ITP, subsequent therapies with less robust evidence include azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone, mycophenolate mofetil, and vinca alkaloids. Splenectomy is recommended only after failure of medical therapies and depends on patient age and comorbidities. For patients who have failed multiple therapies, the panel recommends alemtuzumab, a combined use of initial and subsequent therapies, combination chemotherapy, hematopoietic stem cell transplant, or clinical trials. In emergency situations, antifibrinolytic agents (e.g., tranexamic acid, ε-aminocaproic acid) may be beneficial in preventing recurrent bleeding in patients with severe thrombocytopenia or if bleeding persists despite therapy (particularly in children). In situations of life-threatening bleeding, platelet transfusions may be beneficial. Use of lusutrombopag (Mulpleta) is not addressed in the updated consensus report.

Chronic refractory ITP is defined as failure of response following splenectomy and additional therapy is required. About 20% to 30% of adult patients with ITP have chronic refractory ITP.

The American Society of Hematology (ASH) released an update of the 2011 evidence-based practice guidelines for the management of immune thrombocytopenia in 2019.[13] For newly diagnosed adults who are asymptomatic or have minor mucocutaneous bleeding, ASH suggests treatment with corticosteroids over observation only if the platelet count is $< 30 \times 10^9$/L (conditional recommendation, very low certainty evidence) and recommends management with observation rather than corticosteroid use if the platelet count is $\geq 30 \times 10^9$/L (very low certainty). Treatment decisions should consider the severity of thrombocytopenia, comorbid conditions, use of antiplatelet or anticoagulant drugs, upcoming procedures, and the patient's age. For the management of adults with newly diagnosed ITP, shorter courses of corticosteroids (such as prednisone 0.5 to 2 mg/kg/day or dexamethasone 40 mg/day for 4 days for a total of ≤ 6 weeks) are recommended over longer courses of corticosteroids (> 6 weeks) (very low certainty); corticosteroids alone are suggested as initial therapy in these patients rather than rituximab and corticosteroids (very low certainty). For adults with ITP for ≥ 3 months who are corticosteroid-dependent or unresponsive to steroids who will be treated with a TPO-RA, eltrombopag or romiplostim is suggested (very low certainty). Either splenectomy or a TPO-RA is suggested in adults with ITP for ≥ 3 months who are corticosteroid-dependent or have no response to corticosteroids (very low certainty); however, in these patients rituximab is suggested rather than splenectomy (very low certainty). Furthermore, a TPO-RA is suggested rather than rituximab (very low certainty). The prior 2011

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ASH ITP guidelines addressed the role of IVIG and suggest IVIG be used with corticosteroids if a more rapid increase in platelet count is necessary (grade 2B). Either IVIG or anti-D (in appropriate patients) is suggested as a first-line therapy if corticosteroids are contraindicated (grade 2C). If IVIG is used, the starting dose should be 1 g/kg as a 1-time dose and repeated if needed (grade 2B). Additional research is needed to further evaluate newer agents, such as avatrombopag and fostamatinib. Lusutrombopag is not addressed in the guidelines.

In pediatric patients with no or minor bleeding who are newly diagnosed with ITP, observation is suggested rather than corticosteroids (very low certainty), and observation is recommended rather than IVIG (moderate certainty) or anti-D immunoglobulin (moderate certainty). In newly diagnosed children with non-life-threatening mucosal bleeding and/or decreased health-related quality of life (HRQoL), courses of corticosteroids of ≤ 7 days are recommended over courses > 7 days (very low certainty); and prednisone is recommended (2 to 4 mg/kg per day; maximum, 120 mg daily, for 5 to 7 days) over dexamethasone (0.6 mg/kg per day; maximum, 40 mg per day for 4 days) (very low certainty). Furthermore, corticosteroids are suggested rather than anti-D immunoglobulin (low certainty) and rather than IVIG (low certainty) for these patients. For children with ITP and non-life-threatening mucosal bleeding and/or decreased HRQoL who are unresponsive to first-line treatment, TPO-RAs are suggested rather than rituximab (very low certainty) and rather than splenectomy (very low certainty); however, rituximab is suggested rather than splenectomy (very low certainty).

Thrombocytopenia occurs in 78% of patients with chronic liver disease (CLD) with cirrhosis or fibrosis and in approximately 6% of CLD patients without cirrhosis, making it the most common hematologic abnormality found in patients with CLD.[14,15,16,17] Liver disease-related thrombocytopenia is thought to generally be caused by decreased production (e.g., reduced thrombopoietin), splenic sequestration, and increased destruction of platelets. Patients with CLD often require invasive procedures and are at increased risk of bleed related to the procedures. Interventional management (e.g., partial splenic embolization [PSE], surgical splenectomy) have been used in an attempt to correct splenomegaly-associated thrombocytopenia; however, the only non-invasive tool to increase platelet count is platelet transfusion, which has risks for allergic reaction and infection, as well as iron overload if used chronically. Guidelines are available for platelet transfusions in adults and thrombocytopenia treatment recommendations for patients with cancer or immune (idiopathic) thrombocytopenia (ITP). In addition, in 2020, the American Association for the Study of Liver Diseases (AASLD) published practice guidance on vascular liver disorders, portal vein thrombosis, and procedural bleeding in patients with liver disease.[18] The guidelines discuss avatrombopag and lusutrombopag in relation to the indications for treatment of thrombocytopenia in adults with chronic liver disease scheduled to undergo a procedure; although the agents were superior to placebo for achieving a target platelet level of ≥ 50,000/ µL prior to the procedure, there was not a statistically significant improvement in postprocedural bleeding events compared with placebo. As a result, the guidelines state routine use of these medications for prevention of procedure-related bleeding is not recommended. AASLD states due to the low risk of bleeding of common procedures, risks related to platelet transfusion, lack of evidence that increasing platelet count decreases bleeding risk, and the availability of interventions, such as transfusion and hemostasis in the event of bleeding, both low- and high-risk procedures can reasonably be performed without prophylactically correcting the platelet level. Nonetheless, an individualized approach is recommended for managing patients with severe thrombocytopenia before procedures because definitive evidence for the safety and efficacy of interventions increasing platelet counts in patients with cirrhosis is sparse. The American Gastroenterological Association (AGA) published an expert review in 2019 providing a clinical

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practice update on surgical risk assessment and perioperative management in patients with cirrhosis.[19] Platelet counts > 50,000/µL are generally sufficient for clot formation in the majority of patients with cirrhosis, and prophylactic transfusions in order to raise platelet count may not be helpful and can result in complications (e.g., volume overload, unexpected thrombosis). Avatrombopag and lusutrombopag have been proven efficacious for the treatment of thrombocytopenia in adults with CLD who are scheduled to undergo a procedure. However, the bleeding event rates in the studies were comparable for study drug and placebo, therefore leading to the question of the utility of increasing platelets prior to invasive procedures. Furthermore, these agents carry the potential for thrombotic events (e.g., portal vein thrombosis, other deep vein thromboses). As a result, available literature is unclear on when these agents should be used in cirrhotic patients preoperatively, but it appears reasonable that use may be considered for patients undergoing an elective procedure that is associated with a high bleeding risk, if baseline platelets are < 50,000/µL. Additionally, the AGA coagulation disorders in cirrhosis clinical practice guideline states, for patients with thrombocytopenia and stable cirrhosis undergoing common procedures (e.g., low-risk procedures), routine use of TPO-RAs for bleeding prophylaxis is suggested against (conditional recommendation; very low certainty evidence); however, if there is a high value on uncertain decrease in procedure bleeding and a low value on the increased likelihood for portal vein thrombosis, a TPO-RA can be used.[20]

Aplastic anemia is caused by bone marrow failure.[21] Most cases of aplastic anemia are idiopathic in nature. Initial presentation is often related to anemia or bleeding, although fever or infections may be noted. Symptoms include dyspnea, fatigue, swelling of the feet, gingival bleeding, petechial rashes, infection, headache, and pallor color. Severe or very severe aplastic anemia should be treated promptly. Pharmacotherapy includes immunosuppressive agents (e.g., cyclosporine, methylprednisolone, equine or rabbit antithymocyte globulin, cyclophosphamide, alemtuzumab; all off-label use [except antithymocyte globulin [Atgam®], which is indicated for the treatment of moderate to severe aplastic anemia in patients unsuitable for bone marrow transplantation]), hematopoietic growth factors (eltrombopag, sargramostim [off-label], filgrastim [off-label]), and the antineoplastic agent, fludarabine (off-label).[22] Chelating agents (deferoxamine, deferasirox) may be required in patients chronically transfused due to elevated serum ferritin levels. Nonpharmacologic treatment includes blood transfusions and hematopoietic cell transplant. The major causes of morbidity and mortality from aplastic anemia include infection and bleeding. Approximately 25% to 30% of patients fail to respond to immunosuppressive therapy. Eltrombopag is indicated in patients with severe aplastic anemia who have had an inadequate response to immunosuppressive therapy and as first-line treatment in combination with immunosuppressive agents. Monotherapy with hematopoietic growth factors (e.g., recombinant human erythropoietin [rHuEPO], granulocyte colony-stimulating factor [G-CSF]) is not recommended for newly diagnosed patients.

PHARMACOLOGY[23,24,25,26,27,28,29,30]

Avatrombopag (Doptelet), eltrombopag (Promacta), and lusutrombopag (Mulpleta) are oral TPO-RA that induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

TPO-RAs produce dose- and exposure-dependent platelet increases. With avatrombopag, onset has been reported within 3 to 5 days of the start of a 5-day treatment course, with peak effect occurring after 10 to 13 days. Upon discontinuation of avatrombopag, platelet counts gradually decrease to near baseline values after 35 days. For lusutrombopag, median time to reach maximum platelet count was 12 days (range, 5 to 35).

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Eltrombopag does not affect platelet aggregation or platelet activation. In healthy volunteers, eltrombopag increased platelet counts in a dose-dependent manner with platelet counts rising within 1 to 2 weeks after starting therapy.

Fostamatinib is a spleen tyrosine kinase inhibitor (SYK). *In vivo,* fostamatinib disodium hexahydrate salt converts to its pharmacologically active metabolite, R406, which inhibits signal transduction of Fc-activating receptors and B-cell receptor resulting in reduced antibody-mediated platelet destruction.

Romiplostim (Nplate) increases platelet production through binding and activation of the thrombopoietin receptor in a manner that is similar to endogenous thrombopoietin. Romiplostim is a recombinant thrombopoiesis-stimulating Fc-peptide fusion protein. The peptide portion binds to and activates the human thrombopoietin receptor. Although romiplostim is a competitive thrombopoietin receptor binder, it exerts an enhanced effect on megakaryocytic colony-forming unit growth in the presence of endogenous thrombopoietin. Romiplostim is not identical to endogenous thrombopoietin. Romiplostim produces dose-dependent increases in platelet counts in healthy subjects and in patients with ITP. Platelet counts increase over 4 to 9 days with the peak occurring after 12 to 16 days of a single dose. Platelet counts return to baseline by day 28. Platelets generated by romiplostim have normal platelet function. No change in platelet aggregation has been observed.

PHARMACOKINETICS[31,32,33,34,35]

Drug	Bioavailability (%)	Half-Life	Excretion (%)
avatrombopag (Doptelet)	nd	19 hours	Feces: 88 Urine: 6
eltrombopag (Promacta)	≥ 52	26-35 hours	Feces: 59 Urine: 31
fostamatinib disodium hexahydrate (Tavalisse)	55	15 hours (R406)	Feces: 80 Urine: 20
lusutrombopag (Mulpleta)	nd	27 hours	Feces: 83 Urine: 1
romiplostim (Nplate)	nd	median: 3.5 days range: 1 day to 34 days	Dependent on the thrombopoiesis receptor on platelets

nd = no data

CONTRAINDICATIONS/WARNINGS[36,37,38,39,40]

Contraindications

There are no known contraindications to avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta), fostamatinib (Tavalisse), or romiplostim (Nplate) therapy.

Warnings

Eltrombopag has boxed warnings regarding the risk for hepatotoxicity. Eltrombopag may increase the risk of hepatic decompensation and death when used in combination with interferon and ribavirin in patients with chronic HCV infection. Patients with albumin levels < 3.5 g/dL or a model for end-stage liver disease (MELD) score > 10 are more likely to develop hepatic decompensation and should be monitored. See the Dosage section of this review for monitoring details.

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TPO-RA have been associated with thrombotic and thromboembolic complications, including portal vein thrombosis, in patients with CLD or chronic ITP. In addition, excessive doses of eltrombopag or romiplostim may increase platelet counts to a level that produces thrombotic/thromboembolic complications. Furthermore, there is inadequate evidence to determine a relationship between the maximum platelet level and risk of thrombotic/thromboembolic complications associated with romiplostim. Monitor platelet counts and institute treatment quickly when counts change while using avatrombopag. Use caution when administering avatrombopag, eltrombopag, or lusutrombopag to patients with known risk factors for thromboembolism, such as Factor V Leiden, prothrombin 20210A, antithrombin deficiency, or Protein C or S deficiency. The TPO-RAs and romiplostim should not be administered in an attempt to normalize platelet counts. In clinical trials with eltrombopag in patients with non-ITP thrombocytopenia and chronic liver disease who were undergoing elective invasive procedures, the risk of thrombotic events was increased in patients receiving eltrombopag 75 mg daily. The thrombotic events in the eltrombopag group involved the portal venous system.

Romiplostim stimulation of the thrombopoietin receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies. In clinical trials with romiplostim, progression from myelodysplastic syndromes (MDS) to acute myelogenous leukemia (AML) has been observed. Romiplostim is not indicated for thrombocytopenia due to MDS or any other causes of thrombocytopenia other than ITP. Eltrombopag is not indicated for the treatment of thrombocytopenia due to causes other than persistent or chronic ITP (e.g., chemotherapy or myelodysplasia). In a clinical trial in patients with MDS with thrombocytopenia, the incidence of progression was higher in patients treated with azacitidine plus eltrombopag (12%) compared to azacitidine plus placebo (6%).

Romiplostim may increase the risk for development or progression of reticulin fiber deposition within the bone marrow. The formation may improve upon discontinuation of romiplostim.

Hyporesponsiveness or failure to maintain a platelet response to romiplostim should be investigated; consider investigation for the presence of neutralizing antibodies to romiplostim or bone marrow fibrosis.

Discontinuation of eltrombopag and romiplostim may result in thrombocytopenia of greater severity than was present prior to therapy resulting in an increased bleeding risk, particularly if therapy is discontinued while the patient is on anticoagulants or antiplatelet agents. This worsened thrombocytopenia generally resolves within 14 days following cessation of romiplostim therapy. Therefore, weekly CBCs, including platelet counts, should be monitored for ≥ 2 weeks following discontinuation of romiplostim therapy or for ≥ 4 weeks following discontinuation of eltrombopag. Alternative treatments for worsening thrombocytopenia according to current treatment guidelines may be considered.

Eltrombopag may cause cataracts to develop or worsen in some patients. Perform a baseline ocular examination prior to administration of eltrombopag and during therapy with eltrombopag.

Hypertension, neutropenia, elevated liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin), and diarrhea, including severe cases, have been reported with fostamatinib. Dose interruption, reduction, or discontinuation may be required.

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DRUG INTERACTIONS[41,42,43,44,45]

Avatrombopag (Doptelet) weakly induces cytochrome P450 (CYP) enzymes CYP2C8 and CYP2C9 and inhibits organic anion transporter (OAT) 3 and breast cancer resistance protein (BCRP) *in vitro*. Avatrombopag is a substrate for P-glycoprotein (P-gp) mediated transport. Dose adjustment is necessary for those patients with chronic ITP also taking moderate or strong dual CYP2C9 and CYP3A4 inducers or inhibitors. No dosage adjustments are required in patients with CLD.

Very limited drug interaction studies were performed with eltrombopag (Promacta). Eltrombopag tablets and oral suspension should be taken ≥ 2 hours before or 4 hours after other medications (e.g., antacids), calcium-rich foods (e.g., dairy products, calcium-fortified juices, and certain fruits and vegetables), or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, and zinc. No formal drug interaction studies with romiplostim (Nplate) have been performed.

In vitro studies show that eltrombopag is an inhibitor of the organic anion transporting polypeptide (OATP), OATP1B1, and may increase the systemic exposure of other medications that are substrates of these transporters (e.g., atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, pitavastatin, pravastatin, olmesartan, rosuvastatin, repaglinide, rifampin, simvastatin, valsartan). In clinical trials, a dose reduction of rosuvastatin by 50% was recommended for coadministration with eltrombopag. Use caution with concomitant use of eltrombopag and BCRP substrates (e.g., imatinib, irinotecan, lapatinib, methotrexate, mitoxantrone, rosuvastatin, sulfasalazine, topotecan). Monitor patients for signs and symptoms of excessive exposure to OATP1B1 or BCRP substrates when coadministered with eltrombopag.

According to *in vitro* studies, eltrombopag is also metabolized by CYP1A2 and CYP2C8; therefore, strong inhibitors of these 2 enzymes may result in excessive exposure of eltrombopag. Inhibitors of CYP1A2 include ciprofloxacin and fluvoxamine, and inducers include tobacco and omeprazole. Inhibitors of CYP2C8 include gemfibrozil, trimethoprim, and inducers include rifampin.

Eltrombopag is also an inhibitor of uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15, which are involved with the metabolism of multiple drugs such as acetaminophen, narcotics, and nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical studies have not evaluated the significance of inhibition of these enzymes and the potential for increased systemic exposure of drugs that are substrates of UGT enzymes following their coadministration with eltrombopag. Patients should be monitored closely for signs and symptoms of excessive drug exposure when substrates of the UGT enzymes are administered with eltrombopag.

Eltrombopag chelates polyvalent cations (such as aluminum, magnesium, iron, calcium, zinc, and selenium) in antacids, mineral supplements, and food. In order to avoid significant reductions in eltrombopag due to chelation, the medication should be taken ≥ 2 hours before or 4 hours after of any medications or substances containing polyvalent cations.

For fostamatinib (Tavalisse), CYP3A4 and UGT1A9 are involve in the metabolism of R406. R406 is a substrate of P-gp and can inhibit CYP3A4 and BCRP. Concurrent use of fostamatinib with strong CYP3A4 inhibitors (e.g., ketoconazole) increases the exposure to the major active metabolite of fostamatinib. Dose reductions may be required. Concomitant use with strong CYP3A4 inducers is not recommended due to reduction of fostamatinib metabolite levels. Concomitant use of fostamatinib may increase serum levels of substrates of CYP3A4 (e.g., simvastatin), BCRP (e.g., rosuvastatin), and P-gp (e.g., digoxin). Monitor for toxicities of these agents.

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In *in vitro* studies, lusutrombopag (Mulpleta) demonstrated a low potential to inhibit or induce CYP enzymes or inhibit P-gp, BCRP, or OAT1B enzymes.

Romiplostim (Nplate) may be used with other ITP therapies, including corticosteroids, danazol, azathioprine, IV immunoglobulins, and anti-D immunoglobulins.

ADVERSE EFFECTS[46,47,48,49,50]

Drug	Headache	Diarrhea	Dizziness	Arthralgia	Myalgia	Edema	Increased liver enzymes	
							ALT	AST
avatrombopag (Doptelet)	6-31 (6-14)	nr	nr	13 (0)	0.4	3 (2)	nr	nr
eltrombopag (Promacta)	10-21 (20)	9-19 (2-11)	nr	nr	5-12 (2-10)	10 (5)	5-6 (3)	4 (0-2)
fostamatinib (Tavalisse)	nr	31 (15)	11 (8)	1	nr	nr	11 (0)	9 (0)
lusutrombopag (Mulpleta)	5 (4)	nr	nr	nr	nr	nr	nr	nr
romiplostim (Nplate)	35 (32)	reported	17 (0)	26 (20)	14 (2)	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. Incidences for placebo groups are indicated in parentheses. nr = not reported. ALT = alanine aminotransferase. AST = aspartate aminotransferase.

The most common adverse effects reported with avatrombopag in patients with CLD were (> 3%) pyrexia, abdominal pain, nausea, headache, fatigue, and peripheral edema. In patients with chronic immune thrombocytopenia, headache, fatigue, epistaxis, arthralgia, petechiae, and upper respiratory infection were most commonly reported (> 10%). Hypersensitivity reactions have been reported as a postmarketing adverse effect with avatrombopag.

The most common serious adverse reaction reported while using eltrombopag was hemorrhage, which resulted in discontinuation of therapy. In an open-label trial in which eltrombopag was given in combination with horse antithymocyte globulin (h-ATG) and cyclosporine for first-line treatment of patients with severe aplastic anemia, the following was reported: increased ALT (29%), increased AST (17%), increased bilirubin (17%), rash (8%), and skin discoloration (5%).

Adverse reactions frequently reported in clinical trials with fostamatinib include (fostamatinib versus placebo, respectively): hypertension (28% versus 13%), nausea (19% versus 8%), respiratory infection (11% versus 6%), rash (9% versus 2%), fatigue and chest pain (both 6% versus 2%), and neutropenia (6% versus 0). Mean treatment-related increases of 2.93 mmHg in systolic blood pressure and 3.53 mmHg in diastolic blood pressure over placebo were reported with fostamatinib doses of 100 mg twice daily for 28 days.

Additional adverse effects reported with romiplostim in adults (≥ 10% and greater than placebo) include (rates compared to placebo, respectively): insomnia (16% versus 7%), extremity pain (13% versus 5%), and abdominal pain (11% versus 0). For pediatric patients, the most commonly reported adverse effects include (rates compared to placebo) contusion (41% versus 33%), upper respiratory tract infection (31%

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versus 25%), oropharyngeal pain (25% versus 4%), diarrhea (20% versus 13%), abdominal pain (14% versus 4%), and rash (15% versus 8%). Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported as a postmarketing adverse effect with romiplostim. Erythromelalgia has also been reported in the postmarketing setting.

As with all therapeutic proteins, there is a potential for immunogenicity to develop. In studies with romiplostim, no correlation was apparent between antibody activity and clinical effectiveness or safety.

SPECIAL POPULATIONS[51,52,53,54,55]

Pregnancy

There are insufficient data on use of avatrombopag, eltrombopag, and lusutrombopag in pregnant women to inform of a drug-associated risk to the fetus; however, all were shown to cause fetal harm in animal studies at doses substantially higher than human doses. Pregnant women should be advised of the potential risk of treatment with these agents.

While there are no available data of fostamatinib use in pregnancy, based on findings in animal studies and the mechanism of action, use during pregnancy may cause harm to the fetus. Pregnancy status should be verified prior to starting fostamatinib in females of reproductive potential.

Previously Pregnancy Category C, labeling for romiplostim (Nplate) was updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and advises that based on animal studies, romiplostim may cause fetal harm when administered to a pregnant woman. However, data in pregnant women are inadequate to determine the drug-associated risk for adverse outcomes.

Pediatrics

Eltrombopag is indicated for the treatment of chronic immune thrombocytopenia (ITP) in patients ≥ 1 year of age and in patients ≥ 2 years of age with definitive immunosuppressive therapy (IST)-naïve severe aplastic anemia; however, safety and efficacy in patients < 1 year of age with immune thrombocytopenia or in pediatric patients of any age with thrombocytopenia associated with chronic hepatitis C and refractory severe aplastic anemia have not been established.

Romiplostim is indicated for use in patients ≥ 1 year of age with immune thrombocytopenia for ≥ 6 months who have had an insufficient response other therapies. Additionally, long-term safety of use for a median duration of 3 years was also assessed in a single arm, open-label study in these patients. Serum concentrations of romiplostim were similar in pediatric and adult patients with ITP. Use of romiplostim to increase survival in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation is based on efficacy studies conducted in adult animals; a comparable response to romiplostim is anticipated in the pediatric and adult patients based on the mechanism of action and pharmacokinetics in pediatric patients ≥ 1 year old with ITP.

Safety and efficacy of the remaining agents are not established in pediatric patients.

Geriatrics

Clinical studies for avatrombopag and lusutrombopag did not include adequate numbers of patients ≥ 65 years of age to establish a difference in response to younger patients.

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In clinical studies of eltrombopag and fostamatinib, no overall differences in effectiveness were observed in patients ≥ 65 years of age compared to younger patients.

Romiplostim dose adjustment in the elderly may be needed due to increased prevalence of hepatic, renal, and cardiac impairment. Elderly patients may also have an increased number of concomitant diseases and take multiple medications which can increase the risk for adverse reactions.

Hepatic Impairment

The initial dose of eltrombopag should be reduced when treating patients with persistent or chronic ITP or severe aplastic anemia who also have hepatic impairment.

No dosage adjustments are recommended for avatrombopag, fostamatinib, or lusutrombopag in patients with hepatic impairment.

No clinical studies have been conducted with romiplostim in patients with hepatic impairment.

Renal Impairment

No dosage adjustments are recommended for avatrombopag, fostamatinib, or lusutrombopag in patients with renal impairment.

No clinical studies have been conducted with romiplostim in patients with renal impairment. The effect of renal impairment on unbound (active) eltrombopag exposure has not been assessed.

Race

A reduction in the initial eltrombopag dose may be needed for patients of East-/Southeast-Asian ancestry (Chinese, Japanese, Taiwanese, Korean, or Thai) with ITP (≥ 6 years only) or severe aplastic anemia.

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DOSAGES[56,57,58,59,60]

Drug	Initial Dosing	Titration and/or Dosage timing	Availability
avatrombopag (Doptelet)	**CLD:** Dosing is based on platelet count before a procedure, dose orally for 5 days. ▪ For patients with a platelet count of < 40 × 10^9/L: 60 mg dose (3 tablets) orally once daily. ▪ For patients with a platelet count of 40 × 10^9/L to < 50 × 10^9/L: 40 mg (2 tablets) orally once daily **ITP:** 20 mg tablet orally once daily	**CLD:** Begin treatment 10 to 13 days prior to the scheduled procedure **ITP:** Adjust dose or frequency of dosing to maintain platelet count > 50 x 10^9/L Do not exceed 40 mg per day Discontinue if platelet count is < 50 × 10^9/L after 4 weeks of using 40 mg daily Discontinue if platelet count is > 400 × 10^9/L after 2 weeks of using 20 mg weekly	20 mg tablet
eltrombopag (Promacta)	**ITP** ***patients ≥ 6 years of age:*** 50 mg orally once daily ▪ For patients of East-/Southeast-Asian descent *or* with hepatic impairment (Child Pugh A, B, C): initiate with 25 mg once daily ▪ For patients of East-/Southeast-Asian descent *and* hepatic impairment (Child Pugh A, B, C): initial dose of 12.5 mg once daily may be considered ***patients 1-5 years of age****:* 25 mg orally once daily	Use the lowest dose to achieve and maintain platelet count ≥ 50 × 10^9/L as needed to reduce the risk for bleeding If platelet > 400 × 10^9/L, stop eltrombopag until platelet < 150 × 10^9/L; reinitiate at a 25 mg dose reduction (or at 12.5 mg if the patient was already on 25 mg daily) Discontinue if platelet count is > 400 × 10^9/L after 2 weeks of treatment using the lowest dose **ITP** Increase or decrease the daily dose by 25 mg For patient taking 25 mg once daily increase or decrease the daily dose by 12.5 mg Do not exceed a dose of 75 mg daily Discontinue if platelet count does not increase to a sufficient level to avoid clinically important bleeding after 4 weeks of using 75 mg daily	12.5 mg, 25 mg, 50 mg, 75 mg tablets 12.5 mg, 25 mg oral powder for suspension in unit-dose packets

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Dosages (continued)

Drug	Initial Dosing	Titration and/or Dosage timing	Availability
eltrombopag (Promacta) *continued*	**Chronic HCV-associated thrombocytopenia** 25 mg orally once daily **Aplastic Anemia** **First-line treatment –** Initiate with standard immunosuppressive therapy ***patients ages ≥ 12 years:*** 150 mg once daily for 6 months ***patients ages 6-11 years:*** 75 mg once daily for 6 months ***patients ages 2-5 years:*** 2.5 mg/kg once daily for 6 months ▪ For patients of East-/Southeast-Asian descent *or* with hepatic impairment (Child Pugh A, B, C): decrease dose by 50% **Refractory treatment** 50 mg orally once daily ▪ For patients of East-/Southeast-Asian descent *or* with hepatic impairment (Child Pugh A, B, C): initiate with 25 mg once daily	**Chronic HCV-associated thrombocytopenia** Adjust dose in 25 mg increments every 2 weeks to achieve target platelet count necessary to initiate antiviral therapy Do not exceed 100 mg daily Discontinue eltrombopag when antiviral therapy is stopped **Aplastic Anemia** **First-line treatment** Do not exceed initial dose Do not initiate if ALT or AST are ≥ 5 x upper limit of normal (ULN) Discontinue if ALT or AST > 6 x ULN; may restart at the same dose once ALT or AST are < 5 x ULN or at a 25 mg reduction if levels repeatedly are > 6 x ULN; reduce dose by 25 mg until ALT or AST is < 5 x ULN. In patients < 12 years of age, reduce dose by ≥ 15% to the nearest dose that can be administered For platelet > 200 x 10^9/L to ≤ 400 x 10^9/L: Reduce daily dose by 25 mg in adults and pediatric patient < 12 years of age every 2 weeks to maintain platelet count ≥ 50 x 10^9/L For platelet > 400 x 10^9/L: stop therapy for 1 week, restart when platelet is < 200 x 10^9/L at a daily dose reduced by 25 mg in adults and 12.5 mg in pediatrics < 12 years of age **Refractory treatment** Adjust dose in 50 mg increments every 2 weeks as needed to achieve platelet count ≥ 50 × 10^9/L; if platelets > 400 x 10^9/L, stop therapy for 1 week until platelet < 150 x 10^9/L, restart at dose reduced by 50 mg Do not exceed 150 mg daily May reduce dose by 50% in patients who attain transfusion independence for ≥ 8 weeks; if platelet level remains stable after 8 weeks after dose reduction, then discontinue eltrombopag and monitor platelet count Reinitiate at the previous effective dose for platelets < 30 × 10^9/L, hemoglobin < 9 g/dL, or absolute neutrophil count (ANC) < 0.5 × 10^9/L Discontinue if hematologic response is not seen within 16 week of initiating therapy	

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Dosages (continued)

Drug	Initial Dosing	Titration and/or Dosage timing	Availability
fostamatinib (Tavalisse)	Initial dose is 100 mg orally twice daily	After 1 month, increase to 150 mg twice daily if platelet count is < 50×10^9/L Use the lowest dose to achieve and maintain platelet count ≥ 50×10^9/L Dosage should be reduced, interrupted, or discontinued based on tolerability; a dose-reduction schedule is provided in the product label Discontinue after 12 weeks if platelet count is not adequate to avoid clinically important bleeding	100 mg, 150 mg tablets
lusutrombopag (Mulpleta)	3 mg orally once daily for 7 days	Begin treatment 8 to 14 days prior to the scheduled procedure The procedure should occur 2 to 8 days following the last dose of lusutrombopag	3 mg tablet
romiplostim (Nplate)	**ITP:** Adults and pediatric patients: 1 mcg/kg (based on actual body weight) weekly given by subcutaneous injection Syringes used for injection should have 0.01 mL graduations **HSARS:** Adult and pediatric patients (including term neonates): 10 mcg/kg once as a subcutaneous injection; administer regardless of whether a CBC can be obtained; estimate a patient's absorbed whole body radiation dose based on information from public health officials, biodosimetry, or clinical findings, such as time to onset of vomiting or lymphocyte depletion kinetics	**ITP:** Adjust the weekly dose by increments of 1 mcg/kg until the patient achieves a platelet count ≥ 50×10^9/L as necessary to reduce the risk for bleeding; median dose is 2 mcg/kg weekly; do not dose if platelet count > 400×10^9/L Discontinue if platelet count does not increase after 4 weeks at the maximum weekly dose of 10 mcg/kg; For pediatric patients, reassess body weight every 12 weeks for dose adjustments **HSARS:** administer the dose as soon as possible after suspected or confirmed exposure to radiation levels > 2 gray (Gy)	125 mcg, 250 mcg, 500 mcg vials

Lusutrombopag has only been studied as a single 7-day regimen.

Fostamatinib and lusutrombopag can be taken without regard to food. Take avatrombopag with food.

Eltrombopag should be taken without a meal or with a meal low in calcium (≤ 50 mg). Take at least 2 hours before or 4 hours after other medications, calcium-rich foods, or mineral supplements (calcium, iron, aluminum, magnesium, selenium, zinc).

Patients or caregivers should be instructed on the proper use of the eltrombopag oral suspension to ensure its correct dosing, preparation, and administration. Administer the oral suspension immediately after preparation; discard any unused portion not administered within 30 minutes after preparation.

Modify the dosage regimen of concomitant ITP medications, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

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Patients who have hepatic impairment (Child-Pugh Class A, B, C) may need a reduction in the initial dose of eltrombopag and close monitoring thereafter is warranted. After induction of eltrombopag therapy or an eltrombopag dose increase, prescribers should wait 3 weeks before any further increases in eltrombopag dose.

Administer prepared romiplostim solution within 24 hours using a syringe with 0.01 mL graduations.

Monitoring

To ensure an adequate increase in platelet count, obtain a platelet count before treatment with avatrombopag on the day of a procedure in patients with chronic lung disease (CLD). In patient with chronic immune thrombocytopenia (ITP), assess platelet counts weekly after starting avatrombopag, and then monthly thereafter. After therapy discontinuation, monitor platelet count weekly for at least 4 weeks. Dose adjustments for chronic ITP are detailed in the prescribing information.

With eltrombopag, typically platelet counts increase or decrease within 1 and 2 weeks of starting and stopping therapy, respectively. For eltrombopag, monitor CBC, including platelets, weekly during the dose adjustment phase of therapy with eltrombopag and then monthly following establishment of a stable dose. CBCs should be monitored prior to initiation of therapy, throughout therapy, and following discontinuation (weekly for ≥ 4 weeks) of eltrombopag. Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase, and then monthly once a stable dose has been established. Fractionation should be performed if the patient's bilirubin is elevated. If abnormal levels are detected, the test should be repeated within 3 to 5 days. Serum liver tests should be performed weekly if abnormalities are confirmed until the abnormalities resolve, stabilize, or baseline levels return. Discontinue eltrombopag if ALT levels increase to ≥ 3 times the upper limit of normal (ULN) in patients with normal liver function or are ≥ 3 times the baseline (or > 5 x ULN, whichever is lower) in patients with pretreatment elevated transaminases and are progressive, persistent for ≥ 4 weeks, have increased direct bilirubin, include clinical symptoms of liver injury, or if there is evidence for hepatic decompensation. Hepatotoxicity risks versus benefits must be considered when reinitiating eltrombopag treatment. Weekly serum liver tests should be performed and if test abnormalities continue, worsen, or reoccur, eltrombopag should be permanently discontinued. For first-line treatment of severe aplastic anemia, measure ALT, AST, and bilirubin prior to starting eltrombopag therapy, every other day while hospitalized for horse antithymocyte globulin (h-ATG) therapy, then every 2 weeks during treatment; manage ALT or AST increases as detailed in the product labeling.

Discontinuation of eltrombopag and romiplostim may result in worse thrombocytopenia than was present prior to therapy. Monitor weekly CBCs, including platelet counts, for ≥ 4 weeks after discontinuation of eltrombopag or for ≥ 2 weeks following discontinuation of romiplostim.

For fostamatinib, after obtaining baseline assessments, monitor CBC monthly until a stable platelet count ≥ 50 × 10^9/L is achieved. Bilirubin, ALT, and AST should be monitored monthly. Monitor blood pressure every 2 weeks; if stable, may monitor monthly.

Obtain a platelet count prior to initiation of lusutrombopag therapy and not more than 2 days before the procedure.

In patients treated with romiplostim, CBCs, including platelet counts, should be obtained weekly during the dose adjustment phase, then monthly following establishment of a stable dose, and weekly for ≥ 2 weeks following discontinuation of therapy.

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CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of ≥ 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

avatrombopag (Doptelet) versus placebo

Avatrombopag was evaluated for the treatment of thrombocytopenia in adults with CLD who are scheduled to undergo an elective invasive procedure with anticipated need for a platelet transfusion for procedure-related bleeding in 2 multicenter, randomized, double-blind, placebo-controlled trials, ADAPT-1 (n=231) and ADAPT-2 (n=204).[61,62] In both trials, patients were stratified based on baseline platelet count (cohort-1, < 40 × 10^9/L; cohort-2, 40 × 10^9/L to < 50 × 10^9/L). Patients were then randomized (2:1) to receive 5 daily doses of avatrombopag or placebo; patients in cohort-1 received avatrombopag 60 mg or placebo, while patients in cohort-2 received avatrombopag 40 mg or placebo. Procedures were scheduled 5 to 8 days following the last dose of avatrombopag. The primary efficacy endpoint was the response rate, defined as the proportion of patients who did not require a platelet transfusion or rescue procedure for bleeding following randomization and within 7 days following the procedure. In cohort-1 within ADAPT-1, the response rate was 66% with avatrombopag compared to 23% with placebo (95% confidence interval [CI], 27 to 58; p<0.0001). In cohort-2 within ADAPT-1, the response rate was 88% with avatrombopag compared to 38% with placebo (95% CI, 32 to 68; p<0.0001). In ADAPT-2 cohort-1, the response rate was 69% with avatrombopag compared to 35% with placebo (95% CI, 16 to 52; p=0.0006). In cohort-2 within ADAPT-2, the response rate was 88% with avatrombopag were compared to 33% with placebo (95% CI, 37 to 73; p<0.0001).

eltrombopag (Promacta) versus placebo for ITP

In a phase 3, randomized, multicenter, double-blind, placebo-controlled study, the efficacy, safety, and tolerability of eltrombopag 50 mg daily to 75 mg daily over 6 weeks were evaluated in 114 patients with persistent or chronic ITP.[63,64] Of the 60 patients with a documented time since diagnosis, about 17% were considered to have persistent ITP with time since diagnosis of 3 to 12 months. The patients had platelet counts < 30 × 10^9/L, and 1 or more previous ITP treatments. Standard treatment was continued. Initially patients were randomized to eltrombopag 50 mg daily or placebo. After 3 weeks, patients with platelet counts < 50 × 10^9/L could increase to eltrombopag 75 mg daily. Response was defined as the percentage of patients achieving platelet counts ≥ 50 × 10^9/L at day 43; 59% of eltrombopag-treated patients and 16% of placebo-treated patients achieved response (odds ratio [OR], 9.61; 95% CI, 3.31 to

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27.86; p<0.0001). Median platelet count was 18 × 10^9/L in the placebo group and 69 × 10^9/L in the eltrombopag group. Response to eltrombopag compared with placebo was not affected by predefined study stratification variables (baseline platelet counts, concomitant ITP drugs, and splenectomy status) or by the number of previous ITP treatments. Dose increase to eltrombopag 75 mg daily occurred in 34 out of 73 patients; 10 of the 34 patients had a positive response to eltrombopag treatment. Platelet counts returned to baseline values within 2 weeks after treatment discontinuation. Eltrombopag-treated patients had less bleeding during the study than placebo-treated patients (OR, 0.49; 95% CI, 0.26 to 0.89; p=0.021.)

A randomized, double-blind, placebo-controlled study enrolled 117 patients with persistent or chronic ITP among placebo or 1 of 3 dose regimens of eltrombopag, 30 mg, 50 mg, or 75 mg each administered daily for 6 weeks.[65,66] Of the 51 patients with time since diagnosis, about 14% were considered to have persistent ITP. Patients had baseline platelet counts of < 30 × 10^9/L and had relapsed or were refractory to at least one standard ITP treatment. Primary endpoint was a platelet count of ≥ 50 × 10^9/L on day 43. The primary endpoint was achieved in 2%, 70%, and 81% of the eltrombopag-treated 30 mg, 50 mg, and 75 mg groups, respectively, compared to 11% of the placebo-treated group (p<0.001). The platelet count response to eltrombopag was similar among patients who had or had not undergone splenectomy. In general, increases in platelet counts were detected 1 week following initiation of eltrombopag with the maximum response observed after 2 weeks of therapy. The median platelet counts on day 43 were 26 × 10^9/L in the 30 mg group, 128 × 10^9/L in the 50 mg group, and 183 × 10^9/L in the 75 mg group compared with 16 × 10^9/L in the placebo group. Bleeding events during treatment occurred less often in the eltrombopag 50 mg and 75 mg groups.

The RAISE study, a phase 3, randomized, double-blind, placebo-controlled clinical trial, enrolled 197 adults with previously treated ITP of > 6 months duration who had baseline platelet counts lower than 30 × 10^9/L.[67] Of 145 patients with a time since diagnosis, 19% were considered to have persistent ITP. The study evaluated local standard of care plus eltrombopag 50 mg or placebo once daily for 6 months. Stratification of patients included baseline platelet count (≤ 15 × 10^9/L), use of treatment for immune thrombocytopenia, and splenectomy status. Eltrombopag dose modifications were made based on platelet response. Treatment response was defined as a platelet count of 50 to 400 × 10^9/L and occurred in 79% of patients receiving eltrombopag compared to 28% of patients in the placebo group. The percentage of patients receiving additional treatment was 59% in the eltrombopag-treated group and 32% in the placebo-treated group. Rescue medication was required in 18% of patients on eltrombopag and 40% of patients receiving placebo (p=0.001). Two percent of patients in the eltrombopag group had a thromboembolic event compared to none receiving placebo. Elevations in ALT were reported in 7% and 3% of patients receiving eltrombopag and placebo, respectively. Total bilirubin was reported in 4% of the eltrombopag group and none of the placebo group. Bleeding events were reported in 7% of the patients taking placebo compared to < 1% of the eltrombopag group. The study was supported by the manufacturer of eltrombopag.

eltrombopag (Promacta) versus placebo in pediatrics for ITP

The PETIT2 study, a 2-part, multicenter, placebo-controlled study, evaluated eltrombopag in 92 pediatric patients aged 1 to 17 years with persistent or chronic ITP and platelet counts < 30 × 10^9/L.[68] Patients were stratified by age: 12 to 17 years, 6 to 11 years, and 1 to 5 years. In the double-blind phase, patients were randomized (2:1) to eltrombopag or placebo for the 13 weeks. Initial doses for patients aged 6 to 17 years weight-based and ranged from 50 mg/day and 25 mg/day, depending on ethnic origin. Starting

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dose for patients aged 1 to 5 years was 1.2 mg/kg/day or 0.8 mg/kg/day for East-/Southeast-Asian patients. Patients who completed the double-blind period entered a 24-week, open-label treatment period in which all patients received eltrombopag at either their established dose or the starting dose if they were previously on placebo. The primary outcome of the proportion of patients achieving platelet counts of ≥ 50 × 10^9/L without rescue therapy for ≥ 6 weeks of the 8-week double-blind period was met by 40% of eltrombopag-treated and 3% of placebo-treated patients (odds ratio, 18; 95% CI, 2.3 to 140.9; p=0.0004). Responses were similar in all cohorts. In addition, 37% of patients who received eltrombopag experienced WHO grades 1 to 4 bleeding at the end of the double-blind period compared to 55% who received placebo. During the 24-week open-label treatment period, 80% patients achieved platelet counts of ≥ 50 × 10^9/L at least once.

eltrombopag (Promacta) versus placebo for chronic HCV-related thrombocytopenia

Two randomized, placebo-controlled trials were conducted to evaluate safety and efficacy of eltrombopag for treatment of thrombocytopenia in adults with chronic hepatitis C receiving an antiviral regimen of either peginterferon alfa-2a (n=715) or peginterferon alfa-2b (n=805) in combination with ribavirin.[69] Each study used a 2-phase method consisting of an open-label, pre-antiviral phase and a randomized, antiviral treatment phase. During the pre-antiviral phase of the study, eltrombopag was administered to patients with a platelet count of < 75 × 10^9/L at an initial dose of 25 mg once daily for 2 weeks and then titrated to achieve a platelet count of ≥ 90 × 10^9/L. If target platelet counts were achieved, patients were randomized to either eltrombopag or placebo for the antiviral phase of the study. The primary endpoint for both trials was sustained virologic response (SVR) defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of the antiviral regimen. In both trials, a significantly greater number of patients treated with eltrombopag achieved SVR than those treated with placebo (p<0.05, 23 versus 14% for those receiving peginterferon 2-a and 19% versus 13% for patients peginterferon 2-b).

fostamatinib (Tavalisse) versus placebo

The safety and efficacy of fostamatinib in chronic ITP was studied in 2 double-blind, randomized, placebo-controlled studies referred to as FIT-1 and FIT-2 that were identical in design.[70,71] Patients (n=150) with persistent or chronic ITP, who had an insufficient response to previous treatment were enrolled in the 2 trials. Patients were randomized 2:1 to receive either fostamatinib or placebo for 24 weeks. Randomization was stratified with respect to prior splenectomy and severity of thrombocytopenia. At baseline, the median platelet count was 16 × 10^9/L, and 47% of patients were on stable ITP therapy. Patients initially received fostamatinib at 100 mg twice daily (or matching placebo). At week 4 or later, the dose escalated up to 150 mg twice daily (or matching placebo), based on platelet count and tolerability. Stable concurrent ITP therapy, including glucocorticoids (< 20 mg prednisone equivalent per day), azathioprine, or danazol was allowed, and rescue therapy (e.g., increased dosing of concomitant ITP therapy, immunoglobulin therapy, anti-D, steroids, and platelet infusion) was permitted, if necessary. The study outcome measure was stable platelet response defined as a platelet count of ≥ 50 × 10^9/L on ≥ 4 of the 6 visits between weeks 14 to 24. In the FIT-1 study, 18% of fostamatinib patients versus 0% of placebo patients (p=0.03) achieved the study outcome. In the FIT-2 study, 16% of fostamatinib patients versus 4% of placebo patients achieved the study outcome, which was not statistically significant. Patients who did not respond to treatment after 12 weeks and patients who completed the 24-week study, were eligible to enroll in the FIT-3 open-label extension study (n=123

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patients). Patients who were considered responders in the original study, continued their current trial dose and regimen at rollover; patients were non-responders (platelet < 50×10^9/L) received fostamatinib 100 mg twice daily. Stable response in FIT-3 was defined as a patient initially achieving the target platelet count and then not having 2 visits (≥ 4 weeks apart) with a platelet count < 50×10^9/L, without an intervening visit with a platelet count of ≥ 50×10^9/L (unrelated to rescue therapy), within a period of 12 weeks. Of the 123 subjects, 61 (50%) discontinued the study early. Among patients who achieved stable response in FIT-1, FIT-2, and FIT-3, 18 patients maintained the platelet count of ≥ 50×10^9/L for ≥ 12 months.

lusutrombopag (Mulpleta) versus placebo

The efficacy of lusutrombopag for the treatment of thrombocytopenia in adults with CLD who were scheduled to undergo a procedure was established in 2 randomized, double-blind, placebo-controlled trials, L-PLUS 1 (n=97) and L-PLUS 2 (n=215).[72] In both trials, patients were stratified by liver ablation/coagulation or other procedures and baseline platelet count and were then randomized 1:1 to either lusutrombopag 3 mg or placebo once daily for up to 7 days. The primary efficacy outcome of L-PLUS 1 was the proportion of patients who did not require a platelet transfusion prior to the procedure. The primary efficacy outcome of L-PLUS 2 was the proportion of patients who did not require a platelet transfusion or rescue procedure for bleeding (e.g., platelet preparations, other blood preparations, including red blood cells [RBC] and plasma, volume expanders) following randomization and within 7 days following the procedure. A platelet transfusion was required if the platelet count was < 50×10^9/L. Those who had a platelet count of ≥ 50×10^9/L with an increase of ≥ 20×10^9/L from baseline were considered responders. In L-PLUS 1, the proportion of patients not requiring platelet transfusion prior to the procedure was 78% and 13% in the lusutrombopag and placebo groups, respectively (difference, 64%; 95% [confidence interval] CI, 49 to 79; p<0.0001). The proportion of patients considered responders was 76% in the lusutrombopag group and 6% in the placebo group (difference, 68%; 95% CI, 54 to 82; p<0.0001). In L-PLUS 2, the proportion of patients not requiring platelet transfusion prior to the procedure or rescue therapy for bleeding from randomization through 7 days after invasive procedure was 65% and 29% in the lusutrombopag and placebo groups, respectively (difference, 37%; 95% CI, 25 to 49; p<0.0001). The proportion of patients considered responders was 65% in the lusutrombopag group and 13% in the placebo group (difference, 52%; 95% CI, 41 to 62; p<0.0001). The median (interquartile range [IQR]) duration of platelet count increase to ≥ 50×10^9/L in patients without platelet transfusion was 22 days (IQR, 17 to 27) for patients treated with lusutrombopag and 1.8 days (IQR, 0 to 8.3) in placebo-treated patients in L-PLUS 1. The median (IQR) duration of platelet count increase to ≥ 50×10^9/L in patients without platelet transfusion was 19 days (IQR, 13 to 28) for patients treated with lusutrombopag and 0 days (IQR, 0 to 5) in placebo-treated patients in L-PLUS 2.

romiplostim (Nplate) versus placebo in adults with ITP

In 2 parallel studies, romiplostim was assessed for efficacy in the treatment of chronic ITP among splenectomized and non-splenectomized patients.[73] A total of 63 splenectomized and 62 non-splenectomized adult patients with ITP and a mean of 3 platelet counts 30×10^9/L or less were randomly assigned to romiplostim given subcutaneously (n=42 in splenectomized study and n=41 in non-splenectomized study) or placebo (n=21 in both studies) every week for 24 weeks. Romiplostim was initiated at 1 mcg/kg per week, and doses of romiplostim were adjusted to maintain platelet counts of 50×10^9/L to 200×10^9/L. Prior ITP treatments in both study groups included corticosteroids,

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immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine. Patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the studies. Rescue therapies (e.g., corticosteroids, IVIG, platelet transfusions, and anti-D immunoglobulin) were permitted for bleeding, wet purpura, or if the patient was at immediate risk for hemorrhage. The primary endpoints were measured by a durable platelet response (platelet count ≥ 50 × 10^9/L during 6 or more of the last 8 weeks of treatment) and safety data. Response was achieved by 38% of splenectomized patients given romiplostim versus none of 21 given placebo (difference in proportion of patients responding 38%; 95% CI, 23.4 to 52.8; p=0.0013), and by 61% of non-splenectomized patients given romiplostim versus 5% given placebo (difference in proportion of patients responding 56%; 95% CI, 38.7 to 73.7; p<0.0001). The overall platelet response rate (either durable or transient platelet response) was noted in 88% of non-splenectomized and 79% of splenectomized patients given romiplostim compared with 14% of non-splenectomized and no splenectomized patients given placebo (p<0.0001). Patients given romiplostim achieved platelet counts of > 50 × 10^9/L on a mean of 13.8 weeks (mean 12.3 weeks in splenectomized group versus 15.2 weeks in non-splenectomized group) compared with 0.8 weeks for those given placebo (0.2 weeks versus 1.3 weeks). Concurrent therapy was reduced by 25% or discontinued in 87% of patients given romiplostim (12/12 splenectomized and 8/11 non-splenectomized patients) compared with 38% of those given placebo. Adverse events were similar between groups. Antibodies against romiplostim or thrombopoietin were not detected. Moderate or greater severity bleeding events in the phase 3 trials were more common in the patients treated with placebo (34%) compared to patients treated with romiplostim (15%; p=0.018).[74]

Patients who had participated in either of the 2 adult studies were withdrawn from study medications.[75] If platelet counts subsequently decreased to 50 × 10^9/L or less, the patients were allowed to receive romiplostim in an open-label extension study with weekly dosing based on platelet counts. Following romiplostim discontinuation in the 2 studies, 7 patients maintained platelet counts of ≥ 50 × 10^9/L. A total of 142 patients were enrolled. Patients previously treated with romiplostim received the same starting dose as the final dose given in the previous study, while those in the placebo-arm of the previous study were started on romiplostim 1 mcg/kg. Platelet counts were increased and sustained for up to 156 weeks (median treatment duration of 65 weeks). Overall, 87% of patients reached a platelet count of ≥ 50×10^9/L. Sixty-three percent of patients received romiplostim by self-administration. Serious treatment-related adverse effects and severe bleeding events were each reported in 9% of patients. In the long-term extension study, the incidence of bleeding adverse events of moderate or greater severity decreased from 23% of patients in the first 24 weeks to 12% after 24-48 weeks, remaining ≤ 6% thereafter.[76]

romiplostim (Nplate) versus placebo in pediatrics for ITP

The safety and efficacy of romiplostim in pediatric patients ≥ 1 year of age with ITP for ≥ 6 months was assessed in 2 double-blind, placebo-controlled trials.[77] In both trials, patients were stratified by age and randomized to placebo (n=25 total) or romiplostim (n=59 total) at a starting dose of 1 µg/kg weekly across all ages and titrated over 12 (Study 2) or 24 weeks (Study 1) to maintain platelet count ≥ 50 × 10^9/L to 200 × 10^9/L and not to exceed 10 µg/kg per week. Median age was 9.5 years (range 3 to 17 years) in Study 1 and 10 years in Study 2 (range 1 to 17 years). The majority of patients had ≥ 2 prior ITP therapies (predominantly immunoglobulins and corticosteroids). In Study 1, a single patient in each group had prior splenectomy and in Study 2 this number was 6 in the romiplostim group and 2 in the

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placebo group. In Study 1, the primary efficacy endpoint was proportion of patients who achieved a durable platelet response (≥ 6 weekly platelet counts ≥ 50 × 10^9/L during weeks 18 to 25) and proportion of patients with an overall platelet response (a durable or transient platelet response; transient response was a weekly platelet count ≥ 50 × 10^9/L for ≥ 4 weeks during weeks 2 to 25). For romiplostim versus placebo, the durable response rates were 52% and 10%, respectively, and the overall response rates were 71% and 20%, respectively. The median number of weeks with platelet counts ≥ 50 × 10^9/L was 12 for romiplostim and 1 with placebo. All measurements for romiplostim compared to placebo were significant (p<0.05). In Study 2, the primary efficacy endpoints were the proportion of patients who achieved a platelet count ≥ 50 × 10^9/L for 2 consecutive weeks and proportion of patients who achieved an increase in platelet count ≥ 20 × 10^9/L above baseline for 2 consecutive weeks. Both primary endpoints were achieved in 88.2% (15/17) of patients who received romiplostim compared to no patients treated with placebo.

A single arm, open-label, long-term, 3-year, pediatric study (NCT02279173) evaluated 203 patients with ITP ≥ 6 months before enrollment who had received ≥ 1 prior ITP therapy or were ineligible for other ITP therapies.[78] Romiplostim was given weekly by SC injection beginning at a dose of 1 mcg/kg with weekly increments to a maximum dose of 10 mcg/kg to achieve a target platelet count between 50 x 10^9/L and 200 x 10^9/L. Patients enrolled were a median of 10 years old (range, 1 to 17 years) and were treated for a median duration of 156 weeks. The average percentage of time with a platelet response (≥ 50 x 10^9/L) within the first 6 months of initiation, without rescue medication use for the past 4 weeks, was 50.6%, and the median percentage of time achieving this endpoint was 50%. A total of 29.6% of subjects overall received rescue medications (e.g., corticosteroids, platelet transfusions, IVIG, azathioprine, anti-D immunoglobulin, danazol). The frequency of adverse reactions was similar to those observed in the placebo-controlled clinical studies, with headache occurring in 38% (n=78), 3% (n=6) experiencing severe headache, and 1% (n=2) discontinuing the drug. Changes in bone marrow reticulin and collagen formation were also assessed (n=79) using the modified Bauermeister grading scale. Depending on cohort assignment, patients were assessed at year 1 (cohort 1) or year 2 (cohort 2) compared to baseline bone marrow. A total of 90% of patients in cohort 1 and 73.5% patients in cohort 2 were able to be evaluated with on-study bone marrow biopsies. In cohort 1, increased reticulin fiber formation occurred in 18.5% of patients, and reticulin fiber formation occurred in 47.2% of patients in cohort 2, with a maximum grade of 2. Across both cohorts, no patients developed collagen fibrosis defined as grade 4 or a bone marrow abnormality inconsistent with the underlying diagnosis of ITP.

romiplostim (Nplate) versus standard care

In a randomized, open-label, 52-week, phase 3 study, romiplostim and standard care were compared in 234 adult patients with immune thrombocytopenia who had not undergone splenectomy.[79] Primary outcome parameters were treatment failure and splenectomy. Secondary endpoints included the rate of a platelet response (a platelet count > 50 × 10^9/L at any scheduled visit), safety outcomes, and the quality of life. Patients receiving romiplostim had a significantly lower incidence of treatment failure (11%) than those receiving the standard of care (30%, p<0.001; odds ratio with romiplostim, 0.31; 95% CI, 0.15 to 0.61). Splenectomy also was performed less frequently in patients receiving romiplostim (9%) than in those receiving the standard of care (36%, p<0.001; odds ratio, 0.17; 95% CI, 0.08 to 0.35). For secondary endpoints, the rate of platelet response was higher with romiplostim compared to the standard care group (95% CI, 2 to 2.6; p<0.001). Lower rate of bleeding events and fewer blood transfusions were reported in the romiplostim group compared to the standard care group. Serious

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adverse events were reported in 23% and 37% of the romiplostim and standard care groups, respectively.

romiplostim (Nplate) for HSARS

Due to ethical reasons, efficacy studies evaluating romiplostim could not be conducted in humans with acute radiation syndrome.[80] Therefore, approval for this indication was based on the following: efficacy studies conducted in animals, romiplostim's effect on platelet count in healthy human volunteers, and supporting data in thrombocytopenia in patients with ITP and insufficient response to corticosteroids, immunoglobulins, or splenectomy. Population-based modeling indicated that a single 10 mcg/kg subcutaneous dose of romiplostim would lead to a clinically meaningful effect on the frequency and duration of severe thrombocytopenia in patients acutely exposed to myelosuppressive doses of radiation. Safety for this indication was based on the data from use in patients with ITP as well as from a study with healthy volunteers.

META-ANALYSES

The Cochrane group performed a systematic review of the treatment of chronic ITP to determine the efficacy and safety of the thrombopoietin receptor agonists.[81] Databases searched included Medline, EMBASE, and the Cochrane Central Register of Controlled trials to identify all randomized trials in ITP. Randomized controlled trials were included if the studies evaluated romiplostim or eltrombopag alone or in combination with other drugs, compared to placebo, or splenectomy. Six trials were identified with 808 patients. Five studies compared active treatment to placebo, and one study compared romiplostim to standard of care such as glucocorticoids, anti-D immune globulin, IVIG, rituximab, azathioprine, and others. Overall survival was not studied in these studies. Improvement in significant bleeding events did not reveal any significant differences between the thrombopoietin receptor agonists and the control group (versus placebo risk ratio [RR] 0.48; 95% CI, 0.2 to 1.15; versus standard of care [SOC] risk ratio, 0.49; 95% CI, 0.15 to 1.63). Overall platelet response was statistically improved with romiplostim and eltrombopag compared to placebo and standard of care (versus placebo RR 4.06; 95% CI, 2.93 to 5.63; versus standard of care, RR 1.81; 95% CI, 1.37 to 2.37), complete response (versus placebo RR 9.29; 95% CI, 2.32 to 37.15) and durable response (versus placebo RR 14.16; 95% CI, 2.91 to 69.01). Overall bleeding events were significantly reduced when compared to placebo (RR 0.78; 95% CI, 0.68 to 0.89), but not when compared to standard of care (RR 0.97; 95% CI, 0.75 to 1.26). Authors concluded that there was currently no evidence to support that thrombopoietin receptor agonists are effective in chronic ITP. Compared to placebo or standard of care, romiplostim and eltrombopag significantly increased platelet response, but there was no evidence that bleeding events were improved.

A search of Medline, Embase, and the Cochrane database through July 31, 2018 identified a total of 13 randomized double-blind, placebo-controlled trials in adults (n=1,202 total) with immune thrombocytopenia (ITP) who failed first-line medication or who relapsed after ITP treatment with eltrombopag (6), romiplostim (3), rituximab (2), avatrombopag (1) and fostamatinib (1).82 Duration of treatment ranged from 4 to 24 weeks. Based on pooled data, all products listed, with the exception of rituximab, produced significantly better overall response (OR) compared to placebo. Study authors concluded that romiplostim, eltrombopag, and avatrombopag were superior to rituximab, and romiplostim was superior to fostamatinib. No significant differences in OR were found among the following pairs: romiplostim and eltrombopag, avatrombopag and eltrombopag, eltrombopag and fostamatinib, or fostamatinib and rituximab. Using the surface under the cumulative ranking curve

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(SUCRA) (ranging from 0 to 100), the efficacy hierarchy for OR was determined as highest with romiplostim (SUCRA 87.6%), followed by avatrombopag (82.2%), eltrombopag (65%), fostamatinib (44%), and rituximab (6%). Based on data from 7 of the studies (total 494 patients), early response (ER) was most often reported with avatrombopag (SUCRA 84.5%), then romiplostim (80.8%), eltrombopag (59%), and rituximab (4.1%); ER was not determined for fostamatinib due to lack of data.

A systematic search and network meta-analysis were conducted to evaluate the efficacy and safety of avatrombopag compared to eltrombopag, romiplostim, and fostamatinib for chronic ITP in patients without an adequate response to corticosteroids.[83] Seven phase 3, double-blind, randomized controlled trials met the inclusion criteria for the network meta-analysis. Two of the studies evaluated avatrombopag, 1 evaluated eltrombopag, 2 studies evaluated romiplostim, and 2 evaluated fostamatinib. Placebo was the comparator in 6 of the studies, and the last study compared avatrombopag to eltrombopag; although this study was terminated early due to enrollment issues, data were utilized for safety evaluation. Avatrombopag was found to result in significant improvements compared to placebo in durable platelet response, reduction in the use of concomitant ITP medications, and decreased risk for a bleeding event. Avatrombopag was also found to have a significantly lower incidence of any bleeding events compared to eltrombopag (incidence rate ratio [IRR], 0.38; 95%, credible intervals [CrI], 0.19 to 0.75]) and romiplostim (IRR, 0.38; 95% Crl, 0.17 to 0.86]); other between-treatment differences were not found. Compared to placebo, significant differences were found for durable platelet response and need for rescue therapy with eltrombopag, romiplostim, and fostamatinib. Additionally, compared to placebo, a significant reduction in use of concurrent ITP medication was seen with eltrombopag and romiplostim. The incidence of any bleeding events was also significantly lower with fostamatinib compared to placebo, as was the incidence of WHO grade 2 to 4 bleeding events for both romiplostim and fostamatinib compared to placebo. A significant difference was not found for any adverse events. It was concluded that avatrombopag significantly increased the likelihood for achievement of durable platelet response and reduction in concurrent ITP medication compared to placebo. Additionally, avatrombopag significantly decreased the incidence of any bleeding events compared with placebo, eltrombopag, and romiplostim.

A systematic review and network meta-analysis were conducted to evaluate the efficacy and safety of 5 TPO-RAs in adult patients with thrombocytopenia through indirect comparison of avatrombopag, lusutrombopag, eltrombopag, romiplostim, and recombinant human thrombopoietin (rhTPO).[84] There were no clinical trials with rhTPO versus placebo or the TPO-RAs; therefore, rituximab (RTX) was selected as an intermediate bridge to evaluate the impact of platelet agonists on platelet count. The primary outcome was the number of patients achieving platelet response (platelet levels > 30 to 50 cells x 109/L) without rescue therapy. The secondary outcome was the therapy-related serious adverse reactions and the incidence of bleeding episodes. There were 20 clinical trials with a total of 2,207 patients. Avatrombopag, lusutrombopag, eltrombopag, and romiplostim all demonstrated a significantly better platelet response when compared to the placebo (odds ratio [OR], 36.9 [95% CI, 13.33 to 102.16]; OR, 19.33 [95% CI, 8.42 to 44.4]; OR, 11.92 [95% CI, 7.43 to 19.14]; OR, 3.71 [95% CI, 1.27 to 10.86], respectively). Other arms, RTX + rhTPO and RTX demonstrated no significant differences versus placebo (OR, 1.73 [95 CI% CI, 0.43 to 6.99]; OR, 1.12 [95% CI, 0.48 to 2.61], respectively). The placebo group had the highest probability of bleeding, and lusutrombopag had the lowest risk of bleeding compared to placebo. Adverse reactions were marginally greater in patients administered rituximab versus placebo or other therapies. Avatrombopag was shown to yield the highest efficacy. There were no significant differences observed between avatrombopag and lusutrombopag, or eltrombopag and lusutrombopag;

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however, lusutrombopag showed a significantly improved platelet response versus romiplostim, RTX plus rhTPO, and RTX. Using surface under the cumulative ranking curve (SUCRA) score, avatrombopag was found to be the best treatment for platelet response, followed by lusutrombopag, eltrombopag, romiplostim, rhTPO plus rituximab, rituximab, and lastly, placebo. Pooled results showed that TPO-RAs significantly reduced the incidence of any or severe bleeding events, and lusutrombopag had the lowest risk for any bleeding compared with placebo, followed by eltrombopag, romiplostim, rituximab, and avatrombopag; however, only the lusutrombopag versus placebo comparator met statistical significance.

SUMMARY

Treatment options for immune thrombocytopenia (ITP) include corticosteroids, intravenous immunoglobulin (IVIG), anti-D immunoglobulin, splenectomy, and thrombopoietin receptor agonists (TPO-RA). The spleen tyrosine kinase inhibitor, fostamatinib (Tavalisse), the thrombopoietin receptor agonists (TPO-RA), avatrombopag (Doptelet) and eltrombopag (Promacta), and the recombinant thrombopoiesis-stimulating Fc-peptide fusion protein, romiplostim (Nplate) are indicated for the treatment of thrombocytopenia in patients with ITP who have failed to achieve an adequate response to corticosteroids, immunoglobulins, or splenectomy. These select agents should only be used in patients with ITP who are at risk of bleeding and should not be used for the treatment of thrombocytopenia due to other causes (e.g., chemotherapy, myelodysplasia). Romiplostim is administered as a weekly subcutaneous injection, avatrombopag and eltrombopag are oral tablets dosed once daily, and fostamatinib is an oral tablet dosed twice daily. All 4 agents are indicated in adults; eltrombopag and romiplostim are also approved for use in patients as young as 1 year for ITP.

Eltrombopag (Promacta) is indicated to treat first-line and refractory severe aplastic anemia (including in pediatric patients ≥ 2 years of age) and thrombocytopenia associated with chronic hepatitis C (HCV) interferon-based therapy. It carries a boxed warning regarding the increased risk for hepatic decompensation and death when used in combination with interferon and ribavirin.

The TPO-RAs, avatrombopag (Doptelet) and lusutrombopag (Mulpleta), are indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure. Both are once-daily oral regimens, taken for 5 and 7 consecutive days, respectively.

Romiplostim (Nplate) is also indicated to increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HSARS]). Efficacy for this use was based on studies conducted in animals, the drug's effect on platelet count in healthy humans, and supporting data from thrombocytopenia in patients with ITP and insufficient response to corticosteroids, immunoglobulins, or splenectomy.

The TPO-RAs and romiplostim have been associated with thrombotic and thromboembolic complications, eltrombopag is associated with new or worsening cataracts, and eltrombopag and romiplostim carry the risk of bone marrow reticulin fiber deposits. In addition, fostamatinib, eltrombopag, and romiplostim require frequent hematologic monitoring.

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