

Thrombopoiesis Stimulating Proteins Review

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Thrombopoiesis Stimulating Proteins Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
eltrombopag (Promacta [®]) ¹	GSK	Treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (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.
oprelvekin (Neumega [®]) ²	Wyeth	Prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia. Efficacy was demonstrated in patients who had experienced severe thrombocytopenia following the previous chemotherapy cycle. Neumega is not indicated following myeloablative chemotherapy.
romiplostim (Nplate [™]) ³	Amgen	Treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have failed to achieve an adequate response with corticosteroids, immunoglobulins or splenectomy. Romiplostim should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increases their risk for bleeding.

Overview^{4,5}

Platelets are small, circulating cell particles that do not contain a nucleus. Platelets are released into the bloodstream by megakaryocytes which reside in the bone marrow. Platelet functions include hemostasis. Platelets aggregate and form platelet plugs at sites of injury to limit blood loss.

Thrombocytopenia is generally defined as a platelet count of less than $100 \times 10^9/L$. Thrombocytopenia can result in bruising, bleeding and fatal hemorrhaging. Causes of thrombocytopenia include decreased bone marrow production of megakaryocytes, splenic sequestration of platelets, and increased destruction of platelets.

Following chemotherapy, bone marrow production of megakaryocytes is impaired. For thrombocytopenia related to myelosuppressive chemotherapy, oprelvekin (Neumega) has been shown to prevent severe thrombocytopenia and reduce the need for platelet transfusions in patients receiving myelosuppressive chemotherapy. It is not indicated for primary prevention;

oprelvekin (Neumega) is indicated for patients who have experienced severe thrombocytopenia in a previous chemotherapy cycle.

Idiopathic or immune thrombocytopenic purpura (ITP) has been characterized by a low platelet count. Thrombocytopenia 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 which often occurs two to three weeks after a viral infection or immunization. Spontaneous remission in children typically occurs within two to eight 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; platelet count; patient age; patient's lifestyle related to risk of bleeding; presence of additional risk factors for bleeding, such as uremia, chronic liver diseases, etc.

Not all patients with ITP require treatment. Treatment decisions depend on the presence or absence of bleeding, platelet count and assessment of risk factors for bleeding. In adults, corticosteroids continue to be the first-line therapy for the treatment of ITP. Intravenous gammaglobulin (IVIg) infusions may induce a response faster than corticosteroids; however, platelet counts typically relapse within 11 days of treatment with IVIg. Anti-RhO (D)/anti-D may be an effective alternative; however, these products cannot be used for Rh-negative or postsplenectomy patients. Non-responders are treated with splenectomy. Although not approved for the treatment of ITP, refractory ITP may be treated with azathioprine, cyclophosphamide, cyclosporine, danazol, mycophenolate mofetil, rituximab, or vinca alkaloids. Fibrinolysis inhibitors may be used to reduce excessive mucous membrane hemorrhages, such as nasal, gastrointestinal, and urinary tract bleeding and menorrhagia. Platelet transfusions are effective if no platelet antibodies are present. Massive bleeding is compensated with red cells, fresh-frozen plasma, and platelet concentrates. Chronic refractory ITP is defined as failure of response following splenectomy and additional therapy is required. About 30 percent of adult patients with ITP have chronic refractory ITP.

Until 2009, the definitions, terminology, and outcome parameters of thrombocytopenia have widely varied in clinical trials and literature.⁶ Established by an international working group, ITP now refers to the immune thrombocytopenia (ITP) which requires a platelet count of less than $100 \times 10^9/L$.

Primary ITP is now defined as an autoimmune disorder with isolated thrombocytopenia ($<100 \times 10^9/L$) in the absence of other causes or disorders that might cause thrombocytopenia. The diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy. The main clinical problem of primary ITP is an increased risk of bleeding, although bleeding symptoms may not always be present. Secondary causes of ITP include drug-induced, systemic lupus erythematosus-associated or SLE-associated, and human immunodeficiency virus or HIV-associated. Primary ITP is also defined by the length of time since diagnosis – newly diagnosed (less than three months), persistent (between three and 12 months), and chronic (more than 12 months). Severe ITP, occurring at any time, indicates bleeding which requires treatment or the occurrence of new bleeding symptoms requiring additional treatment or increased dose to control bleeding.

The treatment goal of ITP is to provide a safe platelet count that prevents major bleeding rather

than correcting the platelet count to normal levels. Complete response in clinical trials is now defined as any platelet count of at least $100 \times 10^9/L$. "Response" is defined as any platelet count of 30 to $100 \times 10^9/L$ and at least doubling of the baseline count. "No response" is defined as any platelet count lower than $30 \times 10^9/L$ or less than doubling of the baseline count. The definition of response requires concurrent resolution of bleeding symptoms.

Pharmacology

Eltrombopag (Promacta) is an oral thrombopoietin-receptor agonist which induces proliferation and differentiation of megakaryocytes from bone marrow progenitor cells. 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 one to two weeks after therapy has begun.⁷

Romiplostim (Nplate) increases platelet production through binding and activation of the thrombopoietin receptor in a manner which 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.⁸ 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.⁹ Romiplostim is not identical to endogenous thrombopoietin.¹⁰ Romiplostim produces dose-dependent increases in platelet counts in healthy subjects and in patients with ITP. Platelet counts increase over four to nine 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.

Oprelvekin (Neumega) stimulates megakaryocytopoiesis and thrombopoiesis.¹¹ Oprelvekin improves platelet nadirs and accelerated platelet recovery compared to controls. Platelets produced following oprelvekin are normal in structure, function, and aggregation with a normal life span. In patients with non-myelosuppressive cancer, oprelvekin for 14 days increased the platelet count in a dose dependent manner. Platelet counts increase relative to baseline between five and nine days after oprelvekin is started. After therapy is stopped, platelet counts continue to increase for up to seven days and then return toward baseline levels in 14 days.

Pharmacokinetics

Drug	Bioavailability	Half-Life	Excretion
eltrombopag (Promacta) ¹²	52%	26-35 hours	Feces: 59% Urine: 31%
oprelvekin (Neumega) ¹³ SC administration	> 80%	6.9 hours	Predominantly renal
romiplostim (Nplate) ¹⁴	nd	84 hours	Elimination of romiplostim is dependent on the thrombopoiesis receptor on platelets.

nd = no data

Contraindications/Warnings^{15,16,17}

There are no known contraindications to eltrombopag (Promacta), oprelvekin (Neumega) or romiplostim (Nplate) therapy.

Romiplostim (Nplate) increases the risk for development or progression of reticulin fiber deposition within the bone marrow. Prior to initiation of romiplostim, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Once a stable romiplostim dose has been established, peripheral blood smears and CBCs should be examined monthly for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If new or worsening morphological abnormalities or cytopenia(s) develop, discontinue treatment with romiplostim and consider a bone marrow biopsy, including staining for fibrosis. Discontinuation of romiplostim may result in thrombocytopenia of greater severity than was present prior to romiplostim therapy resulting in an increased the bleeding risk, particularly if romiplostim is discontinued while the patient is on anticoagulants or antiplatelet agents. This worsened thrombocytopenia generally resolves within 14 days; therefore, weekly CBCs, including platelet counts, should be monitored for at least two weeks following discontinuation of romiplostim therapy. Alternative treatments for worsening thrombocytopenia according to current treatment guidelines may be considered.

Excessive doses of romiplostim (Nplate) or medication errors that result in excessive romiplostim doses may increase platelet counts to a level that produces thrombotic/thromboembolic complications; therefore, romiplostim should not be used in an attempt to normalize platelet counts. In addition, romiplostim stimulation of the thrombopoietin receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies.

Eltrombopag (Promacta) administration may cause hepatotoxicity. Measure serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin prior to initiation of eltrombopag, every two weeks during the dose adjustment phase, and monthly following establishment of a stable dose. Discontinue eltrombopag if ALT levels increase to $\geq 3X$ the upper limit of normal (ULN) and are progressive, they persistent for \geq four weeks, are accompanied by increased direct bilirubin, are accompanied by clinical symptoms of liver injury or if there is evidence for hepatic decompensation. Reinitiating treatment with eltrombopag is not recommended.

Eltrombopag is a thrombopoietin (TPO) receptor agonist resulting in the risk for development or progression of reticulin fiber deposition within the bone marrow. Prior to initiation of eltrombopag, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Then examine peripheral blood smears and CBCs monthly for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with eltrombopag and consider a bone marrow biopsy, including staining for fibrosis.

Discontinuation of eltrombopag may result in thrombocytopenia of greater severity than was present prior to therapy with eltrombopag causing an increase in the patient's risk of bleeding, particularly if eltrombopag is discontinued while the patient is on antiplatelet or anticoagulant agents. Following discontinuation of eltrombopag, obtain weekly CBCs, including platelet counts for at least four weeks and consider alternative treatments for worsening

thrombocytopenia, according to current treatment guidelines.

Excessive doses of eltrombopag may cause increases in platelet count resulting in thrombotic/thromboembolic complications. Use caution when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., ATIII deficiency, Factor V Leiden, antiphospholipid syndrome, etc). To minimize the risk for thrombotic/thromboembolic complications, do not use eltrombopag in an attempt to normalize platelet counts.

Eltrombopag stimulation of the TPO receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies. Eltrombopag is not indicated for the treatment of thrombocytopenia due to causes of thrombocytopenia (e.g., chemotherapy or myelodysplasia) other than chronic ITP.

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.

Oprelvekin (Neumega) labeling contains a black box warning regarding allergic reactions including anaphylaxis. Signs and symptoms reported included edema of the face, tongue, or larynx; shortness of breath; wheezing; chest pain; hypotension (including shock); dysarthria; loss of consciousness; mental status changes; rash; urticaria; flushing and fever. Reactions occurred after the first dose or subsequent doses of oprelvekin. Administration of oprelvekin should be permanently discontinued in any patient who develops an allergic or hypersensitivity reaction.

Oprelvekin is not indicated following myeloablative chemotherapy as effectiveness was not demonstrated in a Phase 2 study. Patients receiving oprelvekin in the study reported a statistically significant increase incidence in edema, conjunctival bleeding, hypotension and tachycardia compared to placebo. Fatal adverse events have been reported in patients who received oprelvekin following bone marrow transplantation which included fluid retention or overload, capillary leak syndrome, pleural and pericardial effusion, papilledema and renal failure.

Oprelvekin is associated with serious fluid retention that can result in peripheral edema, dyspnea on exertion, pulmonary edema, capillary leak syndrome, atrial arrhythmias, and exacerbation of pre-existing pleural effusions. Use oprelvekin with caution in patients susceptible to developing congestive heart failure. Fluid retention is reversible within several days following discontinuation of oprelvekin. During dosing with oprelvekin, fluid and electrolyte status should be monitored and appropriate medical management is advised.

Due to an increase in plasma volume secondary to renal sodium and water retention during oprelvekin therapy, dilutional anemia may be observed. Changes are generally 10 to 15 percent reduction in hemoglobin concentration, hematocrit and red blood cell count. The decrease in hemoglobin typically begins within three to five days of the initiation of oprelvekin therapy and is reversible upon discontinuation.

Oprelvekin (Neumega) is associated cardiovascular events including arrhythmias and pulmonary edema. Use with caution in patients with a history of atrial arrhythmias, and only after consideration of the potential risks in relation to anticipated benefit. In clinical trials, cardiac events including atrial arrhythmias (atrial fibrillation or atrial flutter) occurred in 15 percent (23/157) of patients treated with oprelvekin. Approximately one-half (11/24) of the patients who

were rechallenged had recurrent atrial arrhythmias. The mechanism for induction of arrhythmias is not known.

Drug Interactions^{18,19,20}

Very limited drug interaction studies were performed with these agents. No formal drug interaction studies with romiplostim (Nplate) have been performed.

In vitro studies demonstrate that eltrombopag (Promacta) is an inhibitor of the organic anion transporting polypeptide OATP1B1 and can increase the systemic exposure of other drugs that are substrates of this transporter (e.g., atorvastatin, fluvastatin, pravastatin, rosuvastatin, nateglinide, methotrexate, repaglinide, rifampin, benzylpenicillin). In a clinical study of healthy adult subjects, administration of a single dose of rosuvastatin following repeated daily eltrombopag dosing increased plasma rosuvastatin (Crestor[®]) AUC_{0-∞} by 55 percent and C_{max} by 103 percent. Use caution when concomitantly administering eltrombopag and drugs that are substrates of OATP1B1. In clinical trials, a dose reduction of rosuvastatin by 50 percent was recommended for coadministration with eltrombopag.

Eltrombopag chelates polyvalent cations (such as aluminum, magnesium, iron, calcium, zinc, and selenium) in foods, antacids, and mineral supplements. Eltrombopag must not be taken within four hours of any medications or products containing polyvalent cations such as dairy products, antacids, and mineral supplements to avoid significant reduction in eltrombopag absorption due to chelation.

Oprelvekin (Neumega) may be concomitantly administered with filgrastim (Neupogen[®]); no data are available for the use of oprelvekin and sargramostim (Leukine[®]).

Adverse Effects

Drug	Head-ache	Tachycardia	Dizziness	Arthralgia	Myalgia	Edema	Increased liver enzymes	
							ALT	AST
eltrombopag (Promacta) ²¹ n=106	nr	nr	nr	--	3 (1)	nr	2 (0)	2 (0)
oprelvekin (Neumega) ²² n=69	41 (36)	20 (3)	38 (28)	nr	nr	59 (15)	nr	
romiplostim (Nplate) ²³ n=84	35 (32)	nr	17 (0)	26 (20)	14 (2)	nr	nr	

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported. ALT = alanine aminotransferase. AST = aspartate aminotransferase.

Serious adverse effects associated with romiplostim and eltrombopag in clinical studies were bone marrow reticulin deposition and worsening thrombocytopenia after discontinuation. Monitor peripheral blood for signs of marrow fibrosis during eltrombopag therapy. Discontinuation may result in worsened thrombocytopenia than was present prior to eltrombopag and romiplostim therapy. Monitor weekly complete blood counts (CBCs), including platelet counts for at least four weeks after discontinuation of eltrombopag or for at least two weeks following discontinuation of romiplostim.

A complete blood count should be obtained prior to chemotherapy and at regular intervals during oprelvekin (Neumega) therapy. Platelet counts should be monitored during the time of the expected nadir and until adequate recovery has occurred (post nadir counts $\geq 50,000/\text{mCL}$).

Special Populations^{24,25,26}

Pediatrics

Safety and effectiveness have not been established in pediatric patients for any products in this category.

Pregnancy

All products in this category are Pregnancy Category C.

There are no adequate and well-controlled studies of romiplostim or eltrombopag use in pregnant women. A pregnancy registry has been established to collect information about the effects of romiplostim or eltrombopag use during pregnancy. Physicians are asked to register pregnant patients, or pregnant women may enroll themselves in the romiplostim pregnancy registry by calling 1-877-Nplate1 (1-877-675-2831). Physicians are asked to register pregnant patients, or pregnant women may enroll themselves in the eltrombopag pregnancy registry by calling 1-888-825-5249.

Renal Impairment

Oprelvekin (Neumega) is eliminated primarily by the kidneys; therefore, drug exposure of oprelvekin is increased in patients with severe renal impairment (creatinine clearance $< 30 \text{ mL/min}$). Fluid balance should be carefully monitored in patients with renal impairment.

Hepatic Impairment

For patients with moderate and severe hepatic impairment, initiate eltrombopag at a reduced dose of 25 mg once daily. For patients with moderate to severe hepatic impairment, initiate eltrombopag at a reduced dose of 25 mg once daily.

Race

For patients of East Asian ancestry (such as Japanese, Taiwanese, Chinese, or Korean), initiate eltrombopag at a reduced dose of 25 mg once daily.

Dosages^{27,28,29}

Drug	Initial Dosing	Titration	Availability
eltrombopag (Promacta)	50 mg once daily on an empty stomach.	Adjust the dose to achieve and maintain a platelet count $\geq 50 \times 10^9/L$ as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily.	25, 50 mg tablets
oprelvekin (Neumega)	50 mcg/kg daily as a single subcutaneous injection in the abdomen, thigh, or hip.	--	5 mg vial
romiplostim (Nplate)	1 mcg/kg (based on actual body weight) weekly given by subcutaneous injection by enrolled prescribers or healthcare providers under their direction.	Adjust the weekly dose by increments of 1 mcg/kg until the patient achieves a platelet count $\geq 50 \times 10^9/L$ as necessary to reduce the risk for bleeding; do not exceed a maximum weekly dose of 10 mcg/kg. Median dose is 2 mcg/kg weekly	250, 500 mcg vial

Eltrombopag: A 4-hour interval is recommended between eltrombopag administration and administration of other medications, foods, or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium, or zinc

Monitoring^{30,31,32}

For romiplostim, monitor complete blood counts (CBCs), including platelet counts and peripheral blood smears, prior to initiation of romiplostim. During romiplostim therapy, assess CBCs, including platelet count and peripheral blood smears, weekly until a stable platelet count (at least $50 \times 10^9/L$ for at least four weeks without dose adjustment) has been achieved. Complete blood counts, including platelet counts and peripheral blood smears, should be accessed monthly thereafter. In addition, CBCs, including platelet counts, should be performed weekly for at least two weeks following discontinuation of romiplostim therapy. Hyporesponsiveness or failure to maintain a platelet response with romiplostim should prompt a search for causative factors, including neutralizing antibodies to romiplostim or bone marrow fibrosis. To detect antibody formation, submit blood samples to Amgen (1-800-772-6436). Amgen will assay these samples for antibodies to romiplostim and thrombopoietin (TPO). If platelet counts do not increase to a level sufficient to avoid clinically important bleeding after four weeks of romiplostim therapy at the maximum weekly dose of 10 mcg/kg, discontinue therapy.

For eltrombopag (Promacta), monitor CBCs, including platelet counts and peripheral blood smears, weekly during the dose adjustment phase of therapy with eltrombopag and then monthly following establishment of a stable dose. Complete Blood Counts (CBCs) and peripheral blood smears should be monitored prior to initiation, throughout, and following discontinuation (weekly for at least four weeks) of eltrombopag. Monitor serum liver tests (ALT, AST, and bilirubin) prior to initiation of eltrombopag every two weeks during the dose adjustment phase and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation. If abnormal levels are detected, repeat the tests within three to five days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormalities resolve, stabilize, or return to baseline levels. Discontinue eltrombopag for the development of important liver test abnormalities. In controlled clinical studies, cataracts developed or worsened in five patients (five percent) who received eltrombopag 50 mg daily and two (three percent) placebo-group patients. In the extension study, cataracts developed or worsened in four percent of patients who underwent ocular examination prior to therapy with eltrombopag. Cataracts were observed in toxicology studies of eltrombopag in rodents. Patients should undergo a baseline ocular examination prior to administration of eltrombopag and during therapy with eltrombopag; regularly monitor patients for signs and symptoms of cataracts.

Distribution Programs

Only prescribers enrolled in the romiplostim Network of Experts Understanding and Supporting romiplostim and Patients (NEXUS) Program may prescribe romiplostim (Nplate). In addition, romiplostim must be administered by the enrolled prescriber or another health care provider under the direction of the enrolled prescriber.

Eltrombopag is available only through a restricted distribution program called PROMACTA CARES. Under PROMACTA CARES, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive eltrombopag.

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the 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 at least 80 percent 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.

romiplostim (Nplate) versus placebo

In two parallel studies, romiplostim was assessed for efficacy in the treatment of chronic ITP among splenectomized and non-splenectomized patients.³³ A total of 63 splenectomized and 62 non-splenectomized patients with ITP and a mean of three platelet counts $30 \times 10^9/L$ 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 $50 \times 10^9/L$ to $200 \times 10^9/L$. Prior ITP treatments in both study groups included corticosteroids, 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 (i.e., 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 $\geq 50 \times 10^9/L$ during six or more of the last eight weeks of treatment) and safety data. Response was achieved by 38 percent of splenectomized patients given romiplostim versus none of 21 given placebo (difference in proportion of patients responding 38 percent, 95% confidence interval (CI), 23.4 to 52.8, $p=0.0013$), and by 61 percent of non-splenectomized patients given romiplostim versus five percent given placebo (56 percent, 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 percent of non-splenectomized and 79 percent of splenectomized patients given romiplostim compared with 14 percent of non-splenectomized and no splenectomized patients given placebo ($p<0.0001$). Patients given romiplostim achieved platelet counts of $>50 \times 10^9/L$ 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 percent or discontinued in 87 percent of patients given romiplostim (12/12 splenectomized and 8/11 non-splenectomized patients) compared with 38 percent of those given placebo. Adverse events were similar between groups. Antibodies against romiplostim or thrombopoietin were not detected.

Patients who had participated in either of the two studies were withdrawn from study medications.³⁴ If platelet counts subsequently decreased to $50 \times 10^9/L$ 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 two studies, seven patients maintained platelet counts of at least $50 \times 10^9/L$. 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 1 mcg/kg. Platelet counts were increased and sustained for up to 156 weeks (median treatment duration of 65 weeks). Overall, 87 percent of patients reached at least platelet count of $50 \times 10^9/L$. Sixty-three percent of patients received romiplostim by self-administration. Serious treatment-related adverse effects and severe bleeding events were each reported in nine percent of patients.

eltrombopag (Promacta) versus placebo

In a phase III, randomized, multicenter, double-blind, placebo-controlled study, the efficacy, safety, and tolerability of eltrombopag 50 mg daily to 75 mg daily over six weeks were evaluated in 114 patients with chronic ITP.^{35,36} The patients had platelet counts less than $30 \times 10^9/L$, and one or more previous ITP treatments. Standard treatment was continued. Initially patients were randomized to eltrombopag 50 mg daily or placebo. After three weeks, patients with platelet counts less than $50 \times 10^9/L$ could increase to eltrombopag 75 mg daily. Response was defined as the percentage of patients achieving platelet counts $\geq 50 \times 10^9/L$ at day 43; 59 percent of eltrombopag-treated patients and 16 percent of placebo-treated patients achieved response (odds ratio 9.61; 95% CI, 3.31 to 27.86; $p<0.0001$). Median platelet count was $18 \times 10^9/L$ in the placebo group and $69 \times 10^9/L$ 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 two 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 118 patients with chronic ITP among placebo or one of three dose regimens of eltrombopag, 30 mg, 50 mg, or 75 mg each administered daily for six weeks.^{37,38} Patients had baseline platelet counts of $<30 \times 10^9/L$ who had relapsed or were refractory to at least one standard ITP treatment. Primary end point was a platelet count of at least $50 \times 10^9/L$ on day 43. The primary endpoint was achieved in 28 percent, 70 percent, and 81 percent of the eltrombopag-treated 30, 50 and 75 mg groups, respectively compared to 11 percent 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 one week following initiation of eltrombopag with the maximum response observed after two weeks of therapy. The median platelet counts on day 43 were $26 \times 10^9/L$ in the 30 mg group, $128 \times 10^9/L$ in the 50 mg group, and $183 \times 10^9/L$ in the 75 mg group compared with $16 \times 10^9/L$ in the placebo group. Bleeding events during treatment occurred in less often in the eltrombopag 50 and 75 mg groups.

Open-label extension study enrolled patients who completed any prior clinical study with eltrombopag.³⁹ The study goal was to decrease the dose or eliminate the need for any concomitant ITP medications. Eltrombopag was administered to 109 patients; 74 completed three months of treatment, 53 completed six months, and three patients completed one year of therapy. The median baseline platelet count was $18 \times 10^9/L$ prior to administration of eltrombopag. Median platelet counts at three, six, and nine months on study were $74 \times 10^9/L$, $67 \times 10^9/L$, and $95 \times 10^9/L$, respectively. The median daily dose of eltrombopag following six months of therapy was 50 mg ($n=53$); the median daily dose was also 50 mg among patients with no change in the dose regimen of eltrombopag over two months or more of therapy ($n=45$).

oprelvekin (Neumega) versus placebo

The safety and efficacy of oprelvekin in reducing the need for platelet transfusions were evaluated in 77 patients with advanced breast cancer undergoing dose-intensive chemotherapy with cyclophosphamide and doxorubicin plus filgrastim (Neupogen).⁴⁰ Patients were randomized to blinded treatment with oprelvekin 50 mcg/kg/day SC for 10 or 17 days or placebo after the first two chemotherapy cycles. A total of 67 patients were assessable. Oprelvekin significantly decreased the requirement for platelet transfusions; 68 percent of patients who received oprelvekin did not require transfusions, compared with 41 percent in the placebo group ($p=0.04$). Oprelvekin significantly reduced the total number of platelet transfusions required in the assessable subgroup ($p=0.03$) and the time to platelet recovery to more than $50 \times 10^9/L$ in the second cycle ($p=0.01$). Most adverse events in the oprelvekin group were reversible and related to fluid retention.

Summary

Treatment options for immune thrombocytopenia (ITP) include corticosteroids, IVIG, anti-RhO (D)/anti-D immunoglobulin, and splenectomy. Romiplostim (Nplate) and eltrombopag (Promacta) are indicated for the treatment of thrombocytopenia in patients with chronic ITP who

have failed to achieve an adequate response to corticosteroids, immunoglobulins or splenectomy. These agents should only be used in patients with ITP who are at risk of bleeding, and it should not be used for the treatment of thrombocytopenia due to causes other than chronic ITP (e.g., chemotherapy, myelodysplasia). Romiplostim is administered as a weekly subcutaneous injection, and eltrombopag is an oral tablet given daily. Both agents require frequent hematologic monitoring, but eltrombopag also requires frequent hepatic and ocular monitoring. Both agents are available only through restricted distribution programs (PROMACTA CARES and NEXUS program for Nplate).

Oprelvekin (Neumega) is only indicated for the prevention of severe thrombocytopenia and the reduction of the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia. Efficacy was demonstrated in patients who had experienced severe thrombocytopenia following the previous chemotherapy cycle. Patients must be monitored carefully for fluid retention and related adverse effects.

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