

In this Issue...

1

PRIMARY IMMUNE THROMBOCYTOPENIA IN ADULTS AND NEW TREATMENT OPTIONS

5

CE ASSESSMENT QUESTIONS

6

NEW MOLECULAR ENTITIES AND BIOLOGICALS

7

NEW DESCRIPTOR: PRIORITY CLINICAL PRACTICE GUIDELINE 168

Primary Immune Thrombocytopenia in Adults and New Treatment Options

Learning Objectives

1. Define primary immune thrombocytopenia (ITP).
2. Describe when treatment of primary ITP in adults is indicated.
3. Define the place in therapy for eltrombopag and romiplostim in treating adults with primary ITP.
4. Explain specific warnings and precautions for eltrombopag and romiplostim.

Introduction

Primary immune thrombocytopenia (ITP), also frequently referred to as idiopathic thrombocytopenic purpura, is an acquired immune-mediated disease seen in adults and children. The disease is characterized by a transient or persistent peripheral blood platelet count $< 100 \times 10^9/L$, due to increased platelet destruction and decreased or insufficient platelet production.^{1,2} Depending upon the severity of the thrombocytopenia, there is an increased risk of bleeding.^{1,2} The reported incidence of ITP in adults ranges from 1.6 to 2.68 cases/100,000 persons/year with a prevalence of chronic ITP of 23.6 cases/100,000 persons.^{3,4} Women have been shown to have a slightly higher incidence of ITP (1.7:1).⁴ The incidence of ITP also increases with age. There are no reliable and definitive tests for diagnosing ITP. Diagnosis is based on patient history, physical examination, complete blood count with examination of peripheral blood smear, and excluding other causes of thrombocytopenia.⁵ Spontaneous remission occurs in 5 to 11% of adult ITP patients.⁴

Distinguishing between primary and secondary ITP is important as therapy for secondary ITP typically focuses on treating the underlying disease or discontinuing the inducing drug, whereas, if necessary, treatment of primary ITP often begins with immunomodulation.¹ Secondary immune thrombocytopenia includes all forms of immune-mediated thrombocytopenias except primary ITP and includes thrombocytopenias due to an underlying disease or drug exposure, e.g., secondary ITP (systemic lupus erythematosus-associated) or heparin-induced thrombocytopenia (HIT).¹

Persistent ITP is defined as failure to achieve a spontaneous remission or maintain a response after stopping treatment, within 3 to 12 months of diagnosis.¹ Chronic ITP is defined as ITP lasting more than 12 months.¹ A patient with primary ITP who fails to achieve a response to therapy or does not maintain a response after splenectomy, and requires therapy to minimize the risk of clinically significant bleeding, has refractory primary ITP.¹

When to Treat and Goals of Therapy

Treatment for ITP is individualized, taking into account the patient's age, severity of thrombocytopenia and risk of bleeding. All medical and surgical treatments for ITP present the possibility of adverse effects with varying degrees of probability and severity.⁶ The major goal for treatment of primary ITP is not to achieve a normal platelet count (140 to $440 \times 10^9/L$) but to correct the platelet count to a level that prevents major bleeding, with minimal adverse effects.¹ Patients with platelet counts $> 50 \times 10^9/L$ do not typically require treatment.^{5,6}

About the Author:



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Most cases of fatal bleeding related to ITP have occurred in adults with platelet counts $< 30 \times 10^9/L$.¹ Treatment is indicated in adults with platelet counts < 20 to $30 \times 10^9/L$ and in adults who have counts $< 50 \times 10^9/L$ and substantial mucous membrane bleeding or risk factors for bleeding, such as hypertension, peptic ulcer disease, or a potential for substantial trauma to the body.^{5,7}

The risk of fatal and non-fatal bleeding has been shown to increase with age.⁸ The age-adjusted risk of fatal hemorrhage in patients with a platelet count $< 30 \times 10^9/L$ was reported to be 0.4% in adults < 40 years and up to 13% in adults over 60 years of age.⁸ In patients with a platelet count $< 30 \times 10^9/L$, the reported age-adjusted risk of nonfatal major hemorrhage was 3% of patients < 40 years and 71% of patients > 60 years.⁸ The overall mortality rate related to ITP, evaluated in over a dozen studies, ranged from 0.1 to 5%.⁷

First-line and Second-line therapy

First-line treatment of ITP includes corticosteroids, intravenous immune globulin (IVIg), and anti-D immunoglobulin (anti-D) in Rhesus D-positive non-splenectomized patients.^{7,9} Until recently, corticosteroids, IVIg and anti-D were the only medical treatments for patients with ITP approved by the United States Food and Drug Administration (FDA).¹⁰ Oral prednisone or prednisolone 1 to 2 mg/kg/day is the standard initial treatment in non-life-threatening cases requiring treatment.^{2,6} Immunoglobulins are generally recommended for patients with critical bleeding or those unresponsive to corticosteroids.² Splenectomy is a second-line treatment for refractory or corticosteroid-dependent ITP.⁹ A majority of patients, 60-86%, will have a partial or complete response following splenectomy and require no additional therapy. However, approximately 30 to 40% of ITP patients will fail to respond or will relapse following splenectomy.¹¹ An estimated 25 to 30% of chronic ITP patients will not respond to corticosteroids, immunoglobulins, or splenectomy.^{2,9}

Newly Approved Drugs for ITP and Their Place in Therapy

Patients with chronic ITP refractory to drug therapy and splenectomy have the greatest risk of mortality.⁷ Further treatment is recommended for patients with ITP refractory to corticosteroids and splenectomy with platelet count $< 30 \times 10^9/L$ and active bleeding.^{5,6} Two new drugs, romiplostim (Nplate™; Amgen Inc.) administered subcutaneously, and eltrombopag (Promacta®; GlaxoSmithKline) an oral agent, were approved by the FDA in 2008. Both drugs show promise for treating patients with ITP that fails to respond to corticosteroids, immunoglobulins or splenectomy. Unlike corticosteroids and immunoglobulins that decrease destruction of platelets, eltrombopag and romiplostim are thrombopoietin receptor agonists that increase platelet production.

The FDA approved indication is identical for eltrombopag and romiplostim which is: for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.^{12,16} These drugs should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. They should not be used in an attempt to normalize platelet counts. The FDA labeled warnings and precautions for both drugs are also nearly identical, although unique risks and potentially serious side effects for each drug have been identified. Because of limited safety data from clinical trials and the severity of the identified potential side effects, each drug is available only through restricted distribution programs, requiring enrollment of all prescribers and patients.

Romiplostim

Romiplostim is produced in *Escherichia coli* and is a recombinant Fc-peptide fusion protein (peptibody) with 2 thrombopoietin (TPO) receptor-binding domains.¹² Although romiplostim has no amino acid sequence homology to endogenous TPO, it stimulates platelet production through the binding and activation of TPO receptors.

Dosing

The recommended initial once-weekly dose of romiplostim is 1 mcg/kg injected subcutaneously.¹² Thereafter, the once weekly dose is adjusted by 1 mcg/kg increments to achieve and maintain a platelet count $\geq 50 \times 10^9/L$ (see Table 1). Complete blood counts (CBCs), including platelet count and peripheral blood smears, should be done weekly until reaching and maintaining a stable platelet count $\geq 50 \times 10^9/L$ for at least 4 weeks without a dose change, and then at least monthly thereafter. The weekly maximum dose of romiplostim should

Table 1. Weekly Dose Adjustments for Romiplostim¹²

Platelet Count	Dose Adjustment or Response
$< 50 \times 10^9/L$	Increase the dose by 1 mcg/kg.
$> 200 \times 10^9/L$ for 2 consecutive weeks	Reduce the dose by 1 mcg/kg.
$> 400 \times 10^9/L$	Stop romiplostim and assess the platelet count weekly. After the platelet count has fallen to $< 200 \times 10^9/L$, resume romiplostim at a dose reduced by 1 mcg/kg.

not exceed 10 mcg/kg. If, after 4 weeks at a maximum dose of 10 mcg/kg, the patient's platelet count has not recovered to a level sufficient to prevent clinically important bleeding, romiplostim should be stopped.

Pivotal Efficacy Studies

The safety and efficacy of romiplostim was provided in two pivotal 24-week, randomized, double-blind, placebo-controlled studies in 63 splenectomized (Study 20030105) and 62 non-splenectomized (Study 20030212), adult chronic ITP patients who had previously failed to respond adequately to therapy.¹³ Patient platelet counts ranged from 2 to $31 \times 10^9/L$ with a median count $< 20 \times 10^9/L$. Over 25% of the patients continued concomitant therapy with corticosteroids, azathioprine, or danazol. The starting dose of romiplostim was 1 mcg/kg/week and was increased or decreased as needed following an algorithm based on platelet count. Over the 24 weeks, the mean romiplostim dose ranged from 1 to approximately 5.5 mcg/kg/week. The primary efficacy measure was durable response, defined as a platelet count $\geq 50 \times 10^9/L$ during 6 or more weeks of the last 8 weeks of treatment. The durable response rate in romiplostim-treated splenectomized and non-splenectomized patients was 38% (16/42) and 61% (25/41), respectively. The durable response rate in placebo-treated splenectomized and non-splenectomized patients was 0% (0/21) and 5% (1/21), respectively. The difference in the proportion of patients responding to romiplostim versus placebo was significant in both the splenectomized and non-splenectomized patients, 38% (95% confidence interval [CI]: 23.4-52.8; $p = 0.0013$) and 56% (95% CI: 38.7-73.7, $p < 0.0001$), respectively. Absence of splenectomy and weight < 70 kg was associated with a high durable response rate. From pooled safety data for both studies, adverse events were reported in 95% (39/41) of placebo-treated patients and 100% (83/83) of romiplostim-treated patients. Most adverse events were rated as mild to moderate. Headache (35%), fatigue (33%), and epistaxis (32%) and arthralgia (26%) were the most commonly reported adverse events. Significant bleeding events were reported in 12% (5/41) of placebo-

treated patients and 7% (6/84) of romiplostim-treated patients. Two serious adverse events, increased reticulin formation and thrombosis, were considered treatment related.

Major Safety Concerns/ Romiplostim Safety Database

The romiplostim safety database was compiled of information from controlled and uncontrolled studies of 204 chronic ITP patients exposed to romiplostim.¹⁴ Additional safety data came from romiplostim studies for treatment of thrombocytopenia associated with myelodysplasia and cancer chemotherapy.¹⁴ The major safety concerns identified for romiplostim were: reticulin formation and risk for marrow fibrosis, increased risk for hematological malignancy or progression of malignancy, thrombotic risks, re-occurrence of worsened thrombocytopenia after cessation of romiplostim and immunogenicity.¹²

Reticulin Formation

Reticulin is a bone marrow stromal structural fiber that has been associated with many benign and malignant conditions.¹⁴ In the pivotal studies, patients receiving placebo had no reported bone marrow abnormalities, but 1 serious event was reported for 1 patient who received romiplostim. The patient had a history of reticulin fibrosis at the time of study enrollment. A baseline bone marrow sample taken 4 months prior to study entry showed generalized marrow hypoplasia and a mild, patchy increase in reticulin.¹⁴ Romiplostim was then administered weekly over 5 weeks, with a maximum dose of 9 mcg/kg, with no increase in platelet counts above $10 \times 10^9/L$. At week 6, serious, increased reticulin fibrosis with increased nucleated red blood cells was noted. Romiplostim was discontinued and after 3 months, the patient's bone marrow returned to baseline showing a mild, patchy increase in reticulin.¹⁴

The updated romiplostim safety database indicated increased reticulin formation in approximately 4% (9/219) of patients, including 2 patients with localized collagen, a type of bone marrow fiber that has been associated with bone marrow fibrosis and severe hematological complications.¹⁴ Follow-up marrow biopsy results were available for 5 of the 9 patients. Following romiplostim discontinuation, 2 patients had decreased reticulin formation and 3 had stable reticulin findings. Preliminary data from study 20050159, an uncontrolled study of romiplostim in patients with thrombo-cytopenia and myelodysplasia, indicated romiplostim may increase the proportion of blast cells in the peripheral blood of some patients.¹⁴ Of the 44 patients in the initial treatment period and the 25 patients receiving romiplostim in the extension period, 5 withdrew because of progression of myelodysplasia, including 2 progressing to acute myelogenous leukemia and 1 to chronic myelomonocytic leukemia. The other 2 subjects had transient increases in blast cell counts that resolved following discontinuation of romiplostim.

Neoplasia

In the pivotal trials, neoplasia was reported in 2.4% (2/84) of romiplostim-treated patients and 12% (5/41) of placebo-treated patients.¹⁴ Within the romiplostim safety database, neoplasms including B-Cell lymphoma and multiple myeloma were reported in 6% (12/204) of romiplostim-treated patients.¹⁴

Thrombotic Events

Platelet-stimulating drugs may conceivably increase the risk for thromboses. Peripheral arterial embolism and cerebrovascular accident were reported in 2 romiplostim-treated patients versus 1 placebo-treated patient with pulmonary embolism in the pivotal trials.¹⁴ Within the romiplostim safety database, 7% (14/204) of romiplostim-treated patients had a thrombotic event.¹⁴

Table 2. Dose Adjustments for Eltrombopag¹⁶

Platelet Count	Dose Adjustment or Response
< $50 \times 10^9/L$ following at least 2 weeks of eltrombopag	Increase daily dose by 25 mg to a maximum of 75 mg/day.
$\geq 200 \times 10^9/L$ to $\leq 400 \times 10^9/L$ at any time	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> $400 \times 10^9/L$	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once platelet count is < $150 \times 10^9/L$, reinstitute therapy at a daily dose reduced by 25 mg.
> $400 \times 10^9/L$ after 2 weeks of therapy at lowest dose of eltrombopag.	Permanently discontinue eltrombopag.

Recurrent and Worsening Thrombocytopenia

After discontinuing romiplostim in phase 1 and 2 studies, 7% (4/57) of romiplostim treated patients experienced a recurrence of thrombocytopenia with decreases in platelet count below baseline level.¹⁵ Platelet counts returned to baseline level within 14 days of discontinuing romiplostim. Recurrent thrombocytopenia was not addressed in the pivotal studies as the responding patients in these studies were transitioned directly into the open-label extension study.¹⁴

Immunogenicity

Early development of TPO mimetic drugs was complicated by the development of TPO neutralizing antibodies resulting in thrombocytopenia in previously healthy subjects.¹⁴ Eight percent (17/204) of ITP patients exposed to romiplostim developed binding antibodies to romiplostim and 4% (9/204) developed binding antibodies to thrombopoietin.¹⁴ No patient developed neutralizing antibodies to thrombopoietin. One patient with chronic ITP developed neutralizing antibodies to romiplostim. At week 60, tests showed the patient had positive anti-romiplostim binding antibody and negative anti-thrombopoietin and anti-romiplostim neutralizing antibody results. At week 79 when the patient chose to discontinue the study, tests showed the formation of anti-romiplostim binding and neutralizing antibodies but no anti-thrombopoietin binding antibodies. Four months later, anti-romiplostim neutralizing antibodies were undetectable but anti-romiplostim binding antibodies were still present and anti-thrombopoietin antibodies were still negative.

Eltrombopag

Eltrombopag is a small molecule TPO-receptor agonist for oral administration. It interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.¹⁶ The induced signaling cascade is similar to that induced by endogenous TPO, but not identical.

Dosing

The recommended initial adult oral dose for eltrombopag is 50 mg daily, except in patients of East Asian ancestry or in patients with moderate to severe hepatic impairment.¹⁶ In those patients, a starting dose of 25 mg/day is recommended. Eltrombopag should be taken on an empty stomach. Allow a 4 hour interval between eltrombopag and any food, medications or supplements containing polyvalent cations such as iron, calcium, aluminum, magnesium, selenium and zinc. The dose of eltrombopag should be adjusted to maintain a platelet count $\geq 50 \times 10^9/L$ (see Table 2). During therapy with eltrombopag, CBCs, including platelet counts and peripheral blood smears, should be done

weekly until a stable platelet count $\geq 50 \times 10^9/L$ has been attained, then monthly thereafter. The maximum recommended daily dose of eltrombopag is 75 mg. Eltrombopag should be discontinued if: 1) there is an excessive platelet count response (see Table 2) 2) significant liver test abnormalities occur, e.g., alanine aminotransferase (ALT) levels increase to $\geq 3X$ the upper limit of normal and are progressive or 3) after 4 weeks of therapy at the maximum daily dose of 75 mg, the patient's platelet level is not sufficient to avoid clinically important bleeding.

Pivotal Efficacy Studies

Study TRA 100773A and TRA 100773B were the 2 pivotal efficacy studies for eltrombopag.¹⁷ The 2 studies were randomized, controlled studies in adult patients with chronic refractory ITP with platelet counts $< 30 \times 10^9/L$ that had failed at least 1 therapy for ITP. Concomitant corticosteroids were permitted in patients that had been on a stable dose for at least 1 month. The treatment period was 6 weeks with 6 weeks follow-up. The primary efficacy measurement in both studies was the proportion of patients achieving a platelet count $\geq 50 \times 10^9/L$ on day 43. In study TRA 100773A, 118 patients were randomized to receive daily oral eltrombopag 30 mg (n=30), 50 mg (n=30), 75 mg (n=28), or placebo (n=30) for 6 weeks.¹⁸ Forty-seven percent (41/88) of the patients receiving eltrombopag had splenectomy versus 48% (14/29) of placebo treated patients. At day 43, the proportion of patients with a platelet count $\geq 50 \times 10^9/L$ was 11% (3/27) for the placebo group, 28% (8/29) for the 30 mg group, 70% (19/27) for the 50 mg group and 81% (21/26) for the 75 mg group. Ending platelet counts for the 50- and 75-mg groups were significantly better than the placebo group ($p < 0.001$).

In study TRA 100773B, 114 patients were randomized to receive daily eltrombopag 50 mg or placebo for 6 weeks.¹⁷ At baseline, 50% (38/76) of the eltrombopag group and 45% of the placebo group had platelet counts $\leq 15 \times 10^9/L$, respectively. Forty-one percent (31/76) of the eltrombopag-treated patients had previous splenectomy versus 37% (14/38) of placebo-treated patients. At day 43, in the intent-to-treat group, 59% (43/73) of eltrombopag-treated patients versus 16% (6/38) of placebo-treated patients had achieved a platelet count $\geq 50 \times 10^9/L$. Eltrombopag was significantly better than placebo with an odds ratio of 9.61 (95% CI: 3.31-27.86; $p < 0.001$).

In both studies, no significant interaction between treatment response and splenectomy status, age, sex, or race was confirmed although the data for race was limited.¹⁷ Patients with higher baseline platelet counts were more likely to respond to eltrombopag. The pooled most common adverse events were headache (12%), nasopharyngitis (7%), anemia (6%), nausea (6%), fatigue (5%), and diarrhea (5%).¹⁷ Statistical review of the evidence for the ability of eltrombopag to decrease the incidence and severity of bleeding in subjects with relapsed or refractory chronic ITP, showed a trend toward reduced incidence of bleeding for eltrombopag compared to placebo, but was not statistically significant.¹⁹

Major Safety Concerns and the Eltrombopag Safety Database

The safety review of eltrombopag included data from the 2 pivotal studies and from the 120 day safety update from 3, then ongoing, studies in ITP patients: TRA 1053325 (EXTEND), TRA 108057 (REPEAT) and TRA 102537 (RAISE).¹⁷ The safety database for eltrombopag included 330 ITP patients that had been exposed to at least 1 dose of eltrombopag and included 81 patients receiving eltrombopag for ≥ 6 months and 12 patients for ≥ 15 months. The identified risks of eltrombopag, based on clinical studies involving patients with chronic ITP exposed to eltrombopag, include hepatotoxicity, worsened thrombocytopenia compared to baseline, hemorrhage following eltrombopag discontinuation, and cataracts.²⁰ Potential risks for eltrombopag include bone marrow reticulin formation and fibrosis during long-term therapy and increased risk for hematological malignancies, and thrombosis due to excessive platelet increases.¹⁶

Hepatobiliary Toxicity

Hepatic excretion is the primary elimination path for eltrombopag in humans. In the 2 pivotal studies, 9.7% (16/164) of patients that received any dose of eltrombopag showed evidence of hepatobiliary toxicity versus 7.5% (5/67) of placebo-treated patients.¹⁷ Nine percent (29/230) of eltrombopag-treated patients included in the safety database, excluding data from the then ongoing blinded RAISE study, had reported hepatobiliary adverse events meeting FDA criteria for drug-induced liver injury. Prior to initiation of eltrombopag, serum ALT and AST and bilirubin should be measured and then every 2 weeks during the dose adjustment period and monthly following establishment of a stable dose.¹⁶

Recurrent and Worsening Thrombocytopenia Following Therapy

In pivotal study TRA 100773A, transient thrombocytopenia with a platelet count $< 10 \times 10^9/L$ and a decrease in platelet count of at least $10 \times 10^9/L$ compared to baseline was reported within 4 weeks of discontinuation of eltrombopag in 3% (1/30) of the placebo group, 10% (3/30) of the 50 mg group and 7% (2/29) of the 75 mg group.¹⁷ This was also seen in study TRA 100773B, in 11% (8/73) of eltrombopag-treated patients and 8% (3/38) of placebo-treated patients. In 3 of the eltrombopag-treated patients, their post-therapy World Health Organization bleeding scores were also worse and required rescue therapy.¹⁷ In a preliminary report from the uncontrolled REPEAT study, 30 to 41% (20-24/66) of patients experienced worsening thrombocytopenia following discontinuation of eltrombopag.¹⁹ Weekly CBCs, including platelet counts should be done for at least 4 weeks following discontinuation of eltrombopag.¹⁶

Thrombotic Events

One fatality with multiple thromboembolic events reported on autopsy was reported in the clinical trials for eltrombopag.¹⁷ The patient had a history of chronic obstructive pulmonary disease (COPD) and lung cancer. Two weeks after starting eltrombopag with a platelet count of $3 \times 10^9/L$, the patient was admitted with worsening COPD, a grade 4 elevation in liver transaminases and a platelet count of $44 \times 10^9/L$. The patient died 11 days later with a platelet count of $108 \times 10^9/L$. Cause of death was listed as embolism/pulmonary embolism, renal insufficiency and hepatitis, all considered to be related to study medication. Interim data from the uncontrolled EXTEND study reported 7 patients with thromboembolic events.¹⁹

Reticulin Formation

Bone marrow fibrosis and toxicity were not assessed or reported in the pivotal trials for eltrombopag. Interim data from the uncontrolled EXTEND trial indicated 19 patients with a median eltrombopag exposure of 13 months had undergone bone marrow examination. Of these 19 patients, 35% (7/19) had either reticulin (n=5) and/or collagen (n=2) deposition detected.¹⁹

Cataracts

Cataracts developed in lab animals given repeated high doses of eltrombopag.¹⁹ Of the 231 subjects in all treatment groups of the 2 pivotal studies, 161 subjects had 1 or more ocular examinations through which 8 subjects (2 placebo-treated, 5 eltrombopag 50 mg and 1 eltrombopag 75 mg) were identified with cataracts or progression of pre-existing cataracts.¹⁹ Because these studies were short-term and many of the patients entering the studies had risk factors for cataracts, including exposure to corticosteroids, the true risk of eltrombopag in contributing to cataracts in humans is not known. The yet unpublished RAISE trial may help define this risk.

Phototoxicity

Preclinical data for eltrombopag indicated risks for renal toxicity and phototoxicity but limited data from the clinical studies did not provide substantial evidence for these toxicities.¹⁹

(continued on page 8)

ASSESSMENT QUESTIONS



ACCREDITATION INFORMATION



The Collaborative Education Institute (CEI) is accredited by the Accreditation Council for Pharmacy Education as a provider for continuing pharmacy education. The ACPE program number is 107-999-09-045-H01-P, and is a knowledge-based CPE program. CEI will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph. An electronic statement of credit will be awarded upon achieving a passing grade of 70% or better on the exam and completing the program evaluation. Pharmacists must complete this program by April 4, 2012 to receive credit.

Instructions to receive your CE Statement of Credit:

Participants will receive their online CE Statement immediately upon receiving a passing grade on the exam and completing the online program evaluation.

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Click on *Educational Opportunities, Self-Study Programs, Primary Immune Thrombocytopenia in Adults and New Treatment Options; Register*. If you do not yet have a profile on the CEI website, you will be instructed to complete a *Profile*, otherwise enter your user name and password.

After paying the \$7.50 fee, you will receive an email that will direct you to the exam. Upon passing the exam, go back to *My Portfolio*. The title of this article will be listed in your CEI Courses. Select "Evaluation" to the right of the article title and you will be directed to complete the evaluation.

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Again, the 5-step process is listed below:

1. www.TheCEInstitute.org
2. Educational Opportunities, Self-Study Programs, *Primary Immune Thrombocytopenia in Adults and New Treatment Options*, Register
3. Receive email which will guide you to the Exam
4. Evaluation
5. Statement

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Any questions regarding this process should be directed to:

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E/mail: csmith@iarx.org

1. Which of the following statements is false?
 - a. Primary immune thrombocytopenia occurs more frequently in men.
 - b. The estimated prevalence of chronic ITP is about 24 cases/100,000 persons.
 - c. There is no reliable and definitive diagnostic test for ITP.
 - d. Spontaneous remissions of ITP in adults have been reported.
2. The decision to treat ITP should take into account the patient's _____.
 - a. age
 - b. platelet count
 - c. risk of bleeding
 - d. all of the above
3. Which of the following has not been approved by the FDA for treatment of ITP?
 - a. azathioprine
 - b. prednisone
 - c. romiplostim
 - d. eltrombopag
4. The maximum recommended weekly adult dose of romiplostim should not exceed _____.
 - a. 4 mcg/kg
 - b. 6 mcg/kg
 - c. 8 mcg/kg
 - d. 10 mcg/kg
5. The recommended initial daily adult dose of eltrombopag in ITP patients of East Asian ancestry is _____.
 - a. 25 mg twice daily on an empty stomach
 - b. 25 mg daily on an empty stomach
 - c. 25 mg daily with food
 - d. 25 mg three times daily with food
6. Risks identified in clinical studies for eltrombopag include all of the following except _____.
 - a. hepatotoxicity
 - b. cataracts
 - c. worsened thrombocytopenia compared to baseline
 - d. immunogenicity
7. Identified safety concerns for romiplostim include all of the following except _____.
 - a. hepatotoxicity
 - b. thrombotic events
 - c. reticulin formation and risk for marrow fibrosis
 - d. immunogenicity
8. It is recommended that therapy with either romiplostim or eltrombopag be stopped if a patient's platelet count is _____.
 - a. $> 50 \times 10^9/L$
 - b. $> 400 \times 10^9/L$
 - c. $< 50 \times 10^9/L$
 - d. $< 400 \times 10^9/L$
9. Eltrombopag and romiplostim are _____.
 - a. FDA approved first-line therapies in the treatment of ITP
 - b. also recommended to increase platelet counts to a normal level (140 to $440 \times 10^9/L$) in patients with low platelet counts due to adverse drug reaction
 - c. indicated for the treatment of ITP patients that have failed to respond to corticosteroids, immunoglobulins or splenectomy
 - d. also recommended for the treatment of children with chronic refractory ITP
10. What estimated percentage of chronic ITP patients will not respond to therapy with corticosteroids, immunoglobulins or splenectomy?
 - a. 5 to 30%
 - b. 35 to 40%
 - c. 45 to 50%
 - d. 55 to 60%

New Molecular Entities & Biologicals

FDA Approvals
December 2008 – February 2009

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor 155 FDA APPROVAL PACKAGE in combination with the valid drug term to retrieve these documents from the *IDIS* database.

Generic Name Trade Name (FDA Review Classification)	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)	Indication/ Use Dosage Form	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Antithrombin alfa <i>ATryn</i> (BIOL)	GTC Biotherapeutics, Inc. (Feb. 6, 2009)	ANTITHROMBIN III 20120486 (2 citations)	Prevention of perioperative and peri- partum thromboembolic events in hereditary antithrombin deficient patients. Intravenous	Embolism/Thrombosis, VN NEC 453. Prophylaxis NEC V07. Hypercoagulability, BLD, Prim 289.81
Degarelix acetate <i>Degarelix Acetate</i> (S)	Ferring (Dec. 24, 2008)	DEGARELIX 68180908 (4 citations)	Advanced prostate cancer. Powder; subcutaneous	NEOP, MN-Prostate 185.
Eltrombopag olamine <i>Promacta</i> (OP)	GlaxoSmithKline (Nov. 20, 2008)	ELTROMBOPAG 14000055 (21 citations)	Thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura. Oral tablet	Thrombocytopenia, Primary 287.3
Fospropofol disodium <i>Lusedra</i> (S)	Elsai Medcl Res (Dec. 12, 2008)	FOSPROPOFOL 28040020 (14 citations)	Monitored anesthesia care sedation. Intravenous	Anesthesia/Paresthesia 782.0
Gadofosveset trisodium <i>Vasovist</i> (S)	Epix (Dec. 22, 2008)	GADOFOSVESET TRISODIUM 36680062 (7 citations)	Imaging agent for magnetic resonance angiography. Intravenous	Magnetic Resonance imaging 88.9
Milnacipran hydrochloride <i>Savella</i> (S)	Forest Labs (Jan. 14, 2009)	MILNACIPRAN 28160448 (43 citations)	Fibromyalgia Oral Tablet	Myalgia and Myositis NEC 729.1
Plerixafor <i>Mozobil</i> (O,P)	Genzyme (Dec. 15, 2008)	PLERIXAFOR 14000064 (1 citation)	Stem cell mobilization for autologous transplantation patients with non-Hodgkin's lymphoma or multiple myeloma. Subcutaneous solution	Transplant, Stem Cell, Autolog 41.04 Myeloma, Multiple 203. NEOP, MGN-Lymph/Histio NEC 202.
Tapentadol hydrochloride <i>Tapentadol Hydrochloride</i> (S)	Ortho McNeil Janssen (Nov. 20, 2008)	TAPENTADOL 28081320	Moderate to severe acute pain. Oral Tablet	PAIN NEC 780.91

Review Classification:

S=Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs.

AA=Accelerated Approval

FT=Fast Track

P=Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease

BIOL=Biological

O=Orphan



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Selected Bibliography

Degarelix acetate

Gittelman M, Pommerville PJ, Persson BE, et al. A 1-year, open label, randomized Phase II dose finding study of degarelix for the treatment of prostate cancer in North America. *J Urol.* 2008; 180:1986-1992. (IDIS Article Number 605415)

Efficacy and safety of degarelix was assessed in a total of 127 patients, mean age 76 years (range 47-93), with prostate cancer. All patients received a starting dose of 200 mg, and were randomized to receive either 60 or 80 mg in once monthly injections for one year. Median baseline levels of testosterone and prostate specific antigen (PSA) were 4.13 ng/ml (P25-P75 3.03-5.11) and 13.4 ng/ml (P25-P75 6.80-25.7) respectively. At one month after the starting dose, 88% of patients had testosterone levels of 0.5 ng/ml or less. Of those patients, 93% receiving the 60 mg dose and 98% receiving the 80 mg dose had testosterone levels consistently \leq 0.5 ng/ml from one month to one year. In both groups, PSA decreased by 96% after one year, with a median time to 90% reduction of 56 days. Degarelix was well tolerated.

Eltrombopag olamine

Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med.* 2007; 357:2237-2247. (IDIS Article Number 590006)

One hundred eighteen patients, median age 50 years (range 18-85), with idiopathic thrombocytopenic purpura and platelet counts less than 30,000 per cubic millimeter were randomized to 30, 50 or 75 mg oral doses of eltrombopag, or placebo. The primary endpoint was a platelet count of 50,000 or more per cubic millimeter on day 43, and was achieved in the 30, 50 and 75 mg dose groups in 28%, 70% and 81% of patients respectively and in 11% of patients in the placebo group. Bleeding was also reduced in the 50 and 75 mg groups, and adverse events were similar in the study drug and placebo groups.

Gadofosveset trisodium

Perreault P, Edelman MA, Baum RA, et al. MR angiography with gadofosveset trisodium for peripheral vascular disease: Phase II trial. *Radiology.* 2003; 229:811-820. (IDIS Article Number 508907)

This 20-center, randomized study included 238 patients with known or suspected peripheral vascular disease, and compared dose response and safety of gadofosveset trisodium magnetic resonance (MR) angiography with nonenhanced two-dimensional time-of-flight MR angiography and with x-ray angiography. Patients were given gadofosveset trisodium intravenously at doses of 0.005, 0.01, 0.03, 0.05, or 0.07 mmol per kilogram of body weight, or placebo. The study showed that administration of gadofosveset trisodium resulted in a dose-dependent increase in diagnostic accuracy in detecting aortoiliac occlusive disease, as shown in the area under the receiver operating characteristic curve for each reader ($p < 0.001$). There were 121 treatment-related adverse events, three of which were severe.

Milnacipran hydrochloride

Gendreau RM, Thorn MD, Gendreau JF, et al. Efficacy of milnacipran in patients with fibromyalgia. *J Rheumatol.* 2005; 32:1975-1985. (IDIS Article Number 543502)

One hundred twenty-five patients with fibromyalgia, mean ages 46.2-48.0 years, were randomized to placebo or once or twice daily doses of milnacipran to a maximum tolerated dose, with a target dose of 200 mg/day, for three months. Researchers found that both once and twice daily dosing groups showed statistically significant improvement in pain reduction. Side effects were considered mild to moderate and included headache, gastrointestinal complaints, dizziness and exacerbation of hypertension.

Tapentadol hydrochloride

Kleinert R, Lange C, Steup A, et al. Single dose analgesic efficacy of tapentadol in postsurgical dental pain: the results of a randomized, double-blind, placebo-controlled study. *Anesth Analg.* 2008; 107:2048-2055. (IDIS Article Number 608549)

A total of 400 patients undergoing mandibular third molar extraction were randomized to receive a single oral dose of either tapentadol 25, 50, 75, 100 or 200 mg, or morphine sulfate 60 mg, or ibuprofen 400 mg, or placebo for moderate to severe postsurgery pain. Results showed that, compared with placebo, mean total pain relief over 8 hours (TOTPAR-8) was significantly greater for tapentadol 50 mg ($p = 0.041$), 75 mg ($p = 0.001$), 100 mg ($p < 0.001$), and 200 mg ($p < 0.001$); for morphine sulfate 60 mg ($p < 0.001$); and for ibuprofen 400 mg ($p < 0.001$). The reported incidence of nausea and vomiting was lower in all dose groups of tapentadol compared with the morphine sulfate 60 mg group, however the differences were not statistically significant.

NEW DESCRIPTOR

PRIORITY CLINICAL PRACTICE GUIDELINE 168

abbreviation: PRIORITY CLIN PRACT GUIDE

Major category: ARTICLE CLASSIFICATION

Subcategory: DESIGN/ANALYSIS

Evidence-based clinical practice guidelines are systematically developed statements to assist practitioner and patient decisions about health care for specific circumstances. These guidelines are developed by professional societies and associations, national health authorities, and other groups.

To assign descriptor 168, the Iowa Drug Information Service makes an editorial decision to select guidelines that it considers to be of high priority based on several factors including: methodology used for guideline preparation; characteristics of the health condition; potential benefits of guideline implementation; guideline recommendations are presented clearly and graded based on the evidence; and editorial independence of the developer.

For further details of selection criteria see: Moores KG. Evidence-based clinical practice guidelines. In: Malone PM, ed. *Drug Information: A Guide for Pharmacists.* 3rd Ed New York: McGraw Hill, 2006 (Added February, 2009)

Conclusion

Effective treatment options for refractory chronic ITP are limited and reported platelet response rates of 28 to 81% in refractory chronic ITP are remarkable.^{13, 17, 18} Potential serious side effects such as hepatotoxicity, bone marrow reticulin formation potentially leading to myelodysplasia, thrombosis and worsening of thrombocytopenia following therapy must be weighed against the potential benefits. After reviewing and discussing the pivotal studies and the updated safety databases for eltrombopag and romiplostim, members of the 2008 FDA Oncologic Drugs Advisory Committee voted unanimously that these 2 drugs had favorable risk-benefit profiles for some patients with chronic ITP, but there was a need for systematic regular assessment of all patients for significant clinical reactions to these drugs.^{21, 22} Likewise, by approving both drugs, the FDA concurred that the risk-benefit profiles for these drugs was favorable for a specific set of ITP patients. Final reports for the eltrombopag RAISE and REPEAT studies are due in November and April 2009, respectively.²³ Post-marketing commitments for romiplostim and eltrombopag include starting pregnancy exposure registries to compare pregnancy and fetal outcomes, milk lactation studies, and studies to evaluate bone marrow morphology before, during and after therapy.^{23, 24} An antibody registry study for romiplostim is also required.²⁴ As more safety and efficacy data on these 2 drugs is compiled, the future utility of these drugs in treating patients with chronic refractory ITP will become more clear.

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