

CLINICAL THERAPEUTICS

Thrombopoietin-Receptor Agonists for Primary Immune Thrombocytopenia

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.

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A 26-year-old woman with a history of chronic primary immune thrombocytopenia presents for evaluation. Her condition was first diagnosed when she was 11 years of age. Her platelet count has typically been less than 10,000 per cubic millimeter. Her symptoms have not responded to glucocorticoids, and she has had only transient responses to intravenous immune globulin. Previous treatments have included a course of cyclosporine, a course of four doses of rituximab, and splenectomy. Her bleeding symptoms have consisted mainly of menorrhagia, resulting in iron-deficiency anemia. She is currently being treated with a thrombopoietin-receptor agonist, which has resulted in an increase in her platelet count to between 50,000 and 200,000 per cubic millimeter and resolution of her excessive menstrual bleeding, with normalization of her hemoglobin level after iron therapy. She is now inquiring about the long-term treatment of her condition.

THE CLINICAL PROBLEM

Immune (or idiopathic) thrombocytopenia is a disorder that is characterized by immune-mediated platelet destruction and impaired platelet production, resulting in a platelet count of less than 100,000 per cubic millimeter and varying degrees of bleeding risk. The condition is classified as newly diagnosed or transient (during the first 3 months of thrombocytopenia), persistent (3 to 12 months of thrombocytopenia), or chronic (>12 months) on the basis of the time since diagnosis.¹ In primary immune thrombocytopenia, the thrombocytopenia is isolated, whereas in secondary immune thrombocytopenia, the condition is associated with other disorders (e.g., human immunodeficiency virus infection or systemic lupus erythematosus).² The estimated incidence of newly diagnosed primary immune thrombocytopenia is 10 in 100,000 adults per year, distributed equally between the sexes. The rate is increased in the elderly.³ In children, the incidence is thought to be 5 to 6 in 100,000 per year.⁴

Bleeding in immune thrombocytopenia is rare in patients who have a platelet count of more than 50,000 per cubic millimeter. The bleeding risk at lower platelet counts varies greatly from none to very severe, although spontaneous, life-threatening or fatal bleeding is generally confined to patients with a platelet count of less than 10,000 to 20,000 per cubic millimeter.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

In immune thrombocytopenia, immune dysregulation leads to the production of auto-antibodies or immune complexes that accelerate peripheral platelet destruction by

binding to platelets, causing platelet phagocytosis, along with T-cell and possibly complement-mediated lysis.⁵⁻⁷ The production of new platelets is also suppressed; antiplatelet antibodies have been shown to bind to megakaryocytes in the bone marrow, causing both a decrease in the number of megakaryocytes and the inhibition of megakaryocyte maturation.⁸

Thrombopoietin is the humoral regulator of platelet production.⁹ Endogenous thrombopoietin, which is produced mainly in the liver, binds and activates specific thrombopoietin receptors on the membrane of the megakaryocyte and induces cytoplasmic signaling for platelet production (Fig. 1).¹⁰ Plasma levels of endogenous thrombopoietin are typically high in patients who have thrombocytopenia associated with bone marrow failure syndromes. However, thrombopoietin levels are usually normal or only slightly increased in patients with immune thrombocytopenia, for reasons that remain unclear.¹¹

The fact that thrombopoietin levels in immune thrombocytopenia are lower than anticipated led to the concept of treating the disorder by means of exogenous stimulation of thrombopoietin receptors. Initial trials involved the use of recombinant forms of thrombopoietin.^{12,13} However, clinical trials were stopped when thrombocytopenia — resulting from the development of autoantibodies against endogenous thrombopoietin — developed in healthy volunteers receiving these agents.¹⁴

Thus, development began on a second generation of thrombopoietin mimetics or agonists that are structurally dissimilar to thrombopoietin and thus do not lead to the formation of autoantibodies. Romiplostim (Nplate, Amgen) is a synthetic fusion protein that has four peptides consisting of 14 amino acid residues connected to an IgG Fc fragment, producing a “peptibody” (Fig. 1A).¹⁵ Romiplostim binds to the thrombopoietin receptor and activates intracellular signaling pathways (the JAK-STAT and MAP kinase pathways), which stimulates platelet production. Eltrombopag (Promacta, GlaxoSmithKline) is a small nonpeptide molecule¹⁵ that binds to the transmembrane region of the thrombopoietin receptor, which activates the same intracellular pathways that are activated by romiplostim (Fig. 1B).

In initial pharmacodynamic studies, a single intravenous or subcutaneous dose of romiplostim resulted in an increase in the platelet count after 5 to 8 days in a dose-dependent fashion (Fig. 2).¹⁶

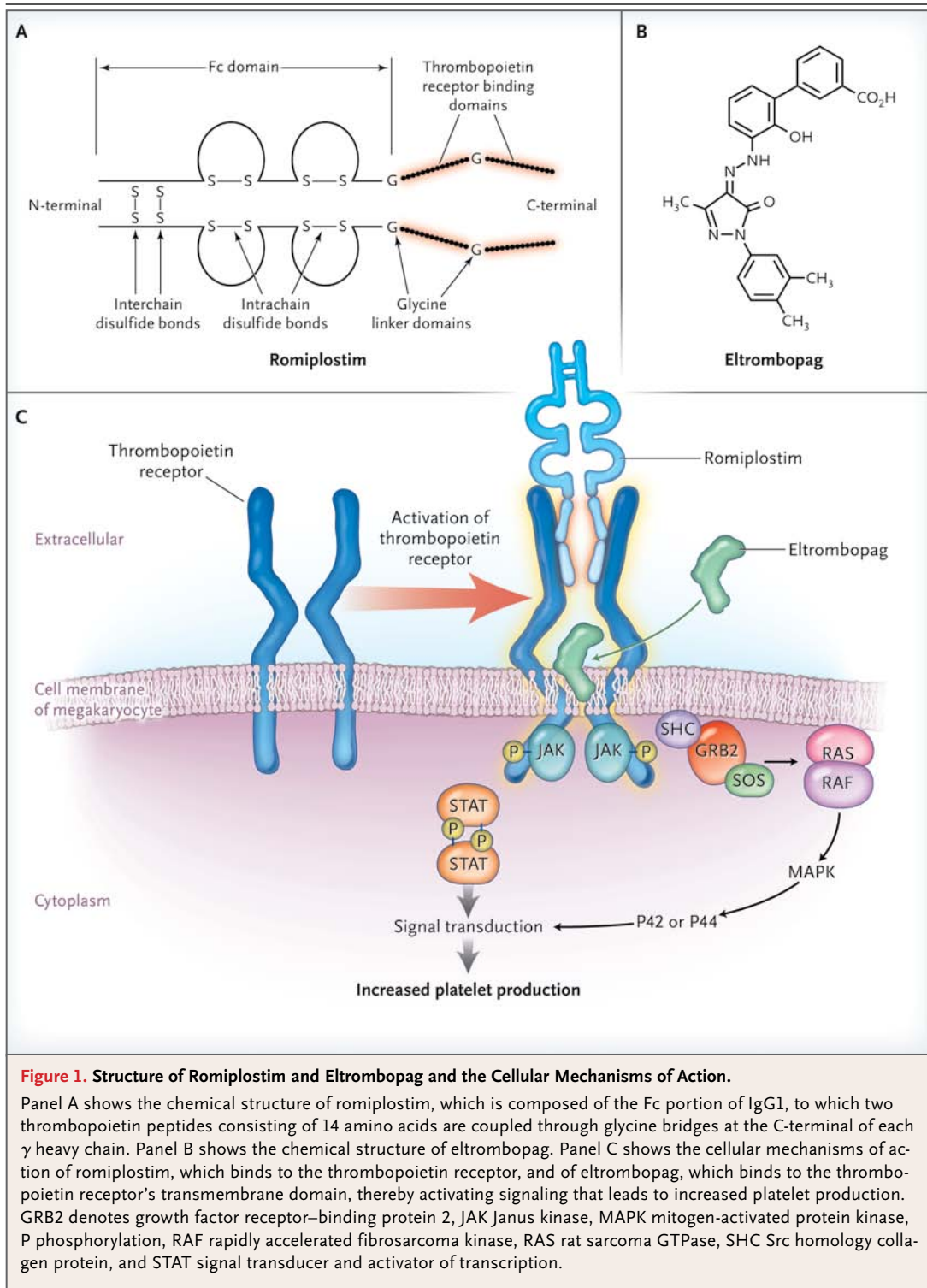
The peak platelet count was reached between days 12 and 16, and by day 28 the platelet count had fallen to baseline. Eltrombopag has shown a similar pattern of response in platelet count.

CLINICAL EVIDENCE

Clinical studies of both romiplostim and eltrombopag were conducted in adults with refractory immune thrombocytopenia and a platelet count of less than 30,000 per cubic millimeter, including patients who had undergone previous splenectomy.

The romiplostim trials included two 24-week placebo-controlled phase 3 studies, one enrolling 63 splenectomized patients and the other enrolling 62 nonsplenectomized patients.¹⁷ The primary efficacy end point was a durable response, which was defined as a platelet count of at least 50,000 per cubic millimeter for at least 6 of the final 8 weeks. This end point was achieved in 38% of splenectomized patients and in 61% of nonsplenectomized patients in the romiplostim groups, as compared with no splenectomized patients and 5% of nonsplenectomized patients in the placebo groups ($P < 0.001$ for both comparisons). Patients receiving romiplostim were more likely to reduce or discontinue concurrent medications (primarily glucocorticoids) and to require less rescue medication than patients in the placebo group. In an ongoing open-label extension study involving 292 patients, 94.5% achieved a platelet count of at least 50,000 per cubic millimeter during the study, and more than 50% had a platelet count of at least 50,000 per cubic millimeter during at least 90% of all visits at a median of 78 weeks.¹⁸

Eltrombopag was approved by the Food and Drug Administration (FDA) on the basis of the results of two 6-week, placebo-controlled clinical trials and the initial results of an open-label extension study. The primary efficacy measurement in both randomized studies was the proportion of patients achieving a platelet count of at least 50,000 per cubic millimeter on day 43. In a dose-adjustment study involving 118 patients, this platelet count was achieved more often in the groups who received daily oral eltrombopag (at a dose of either 50 mg or 75 mg) than in those receiving placebo.¹⁹ In a subsequent phase 3 placebo-controlled trial involving 114 patients who were treated with 50 mg of eltrombopag per day, a platelet count of at least 50,000 per cubic millimeter was achieved by day 43 in 59% of patients in the eltrombopag group,



as compared with 16% of those in the placebo group ($P < 0.001$).²⁰ In an ongoing open-label extension study involving 299 patients who completed a previous eltrombopag study, 87% of patients

achieved a platelet count of at least 50,000 per cubic millimeter during treatment.²¹

Both romiplostim and eltrombopag have been found to reduce bleeding complications. In the

romiplostim extension study, the rate of moderate-to-severe bleeding decreased from 23% to 12% within the first 24 weeks and to 6% during weeks 24 through 48.²² In the eltrombopag extension study, the incidence of any bleeding symptoms declined from 56% at baseline to 16% by week 52 and to 20% by week 104.²¹

CLINICAL USE

The goal of treatment in patients with immune thrombocytopenia is to maintain the platelet count at a level that reduces the risk of bleeding with minimal treatment-related toxic effects. Observation alone is recommended when no or mild bleeding is present and the platelet count is more than 30,000 per cubic millimeter in adults.²³ Treatment in patients with a lower platelet count is indicated only if bleeding occurs or if the platelet count is very low. (For example, most experts would treat a nonbleeding patient who had a platelet count of <10,000 per cubic millimeter.)

Initial treatment for immune thrombocytopenia is generally a course of glucocorticoids, intravenous immune globulin, or both. The only second-line treatment that has been shown to produce sustained increases in the platelet count is splenectomy.²³ Rituximab is widely used as a second-line agent, although the median duration of response with this agent is only 10.5 months.²⁴

Romiplostim and eltrombopag are approved by the FDA for patients with chronic immune thrombocytopenia who have an insufficient response to glucocorticoids, intravenous immune globulin, or splenectomy. Clinically, these agents are typically used in patients who have persistent or chronic immune thrombocytopenia and ongoing bleeding, with or without previous splenectomy and one or more courses of rituximab. Since thrombopoietin-receptor agonists cross the placenta, their safety in pregnancy has not been shown, so their use in such cases is not recommended.

The recommended initial dose of romiplostim is 1 μg per kilogram of body weight, administered subcutaneously once weekly, with subsequent dose adjustment on the basis of the platelet count. The mean therapeutic dose is 3 to 4 μg per kilogram, with a maximum dose of 10 μg per kilogram. Romiplostim is available in 250- μg and 500- μg vials as a lyophilized powder. The terms of the FDA approval of romiplostim in the United States specify that the drug cannot be administered by

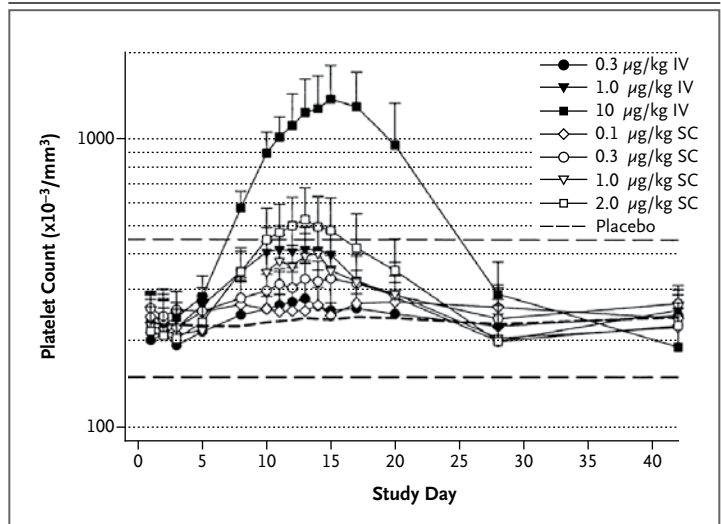


Figure 2. Platelet Counts in Healthy Subjects Receiving Various Doses of Romiplostim, as Compared with Placebo.

Shown are mean platelet counts in healthy subjects receiving a single intravenous (IV) or subcutaneous (SC) bolus dose of romiplostim or placebo (with 8 subjects receiving 2.0 g of romiplostim subcutaneously, 4 subjects receiving all other doses of romiplostim, and 16 subjects receiving placebo). The dashed lines show the normal range for the platelet count (150,000 to 450,000 per cubic millimeter). Reprinted with permission from the publisher.¹⁶

the patient, but rather must be given by a health care provider. Furthermore, only providers who are enrolled in a regulated prescriber program called NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) may prescribe romiplostim. The NEXUS program requires providers to enroll all patients receiving romiplostim in a registry and to enter baseline data for patients as well as periodic safety information. Details regarding the NEXUS program are available at www.nplatenexus.com. These restrictions do not apply to the use of romiplostim outside the United States. In most other countries, the drug can be self-administered by the patient at home.

The recommended initial dose of eltrombopag for most patients is 50 mg daily given orally, with subsequent dose adjustment on the basis of the platelet count (to a maximum of 75 mg daily or a minimum of 25 mg daily). Patients with hepatic dysfunction and patients of Asian ethnic background (in whom plasma concentrations of the drug are higher than in white patients) should initiate treatment at a dose of 25 mg once daily. Eltrombopag should be taken 1 to 2 hours after a meal because of interactions with food. It should not be taken within 4 hours after taking antacids,

dairy products, or supplements that contain polyvalent cations, such as calcium, magnesium, and aluminum. Like romiplostim, eltrombopag was approved by the FDA under restricted terms. In the United States, the drug can be prescribed only by participants in a regulated prescriber program called Promacta Cares. Details regarding the program are available at www.promactacares.com.

When either romiplostim or eltrombopag is given, the platelet count should be measured weekly until a stable count (>50,000 per cubic millimeter for at least 4 weeks without dose adjustment) has been achieved and monthly thereafter. Treatment should be withheld temporarily when the platelet count is 200,000 to 400,000 per cubic millimeter; it is not a goal of therapy to achieve and maintain a normal platelet count.

Eltrombopag therapy can cause hepatic injury (see Adverse Effects below). Thus, patients receiving eltrombopag should have levels of serum aspartate aminotransferase, alanine aminotransferase, and bilirubin checked every 2 weeks during the dose-adjustment phase of therapy and monthly after the establishment of a stable dose.

Estimated costs of treatment with romiplostim for a patient weighing 75 kg at a dose of 3 μ g per kilogram weekly are approximately \$5,313 per month in the United States,²⁵ £1,928 per month in the United Kingdom,²⁶ and 4,244 CHF per month in Switzerland. Estimated costs of treatment with eltrombopag at a dose of 50 mg daily are approximately \$3,960 per month in the United States,²⁷ £1,540 per month in the United Kingdom,²⁸ and 3,268 CHF per month in Switzerland.

ADVERSE EFFECTS

The most common adverse effects of thrombopoietin-receptor agonists in clinical trials included headache, nausea, vomiting, fatigue, diarrhea, arthralgia, and nasopharyngitis.^{17,20} Worsened thrombocytopenia after the discontinuation of the thrombopoietin-receptor agonist occurs in 8 to 10% of patients, with an increased risk of bleeding during the first 4 weeks.^{17,20} Tapering of the agent or reinitiation of other treatment for immune thrombocytopenia is recommended if severe thrombocytopenia supervenes. The platelet count typically recovers to pretreatment levels after several weeks.

In prospective studies, patients receiving eltrombopag had hepatobiliary laboratory abnor-

malities; 11% of patients receiving eltrombopag and 7% receiving placebo had aminotransferase values at least 3 times the upper limit of the normal range and alkaline phosphatase or total bilirubin values at least 1.6 times the upper limit of the normal range.²⁹ These abnormalities may resolve despite continued therapy. However, the package insert specifies that eltrombopag therapy should be discontinued if alanine aminotransferase levels increase to 3 times the upper limit of the normal range or higher and are progressive, are persistent for 4 weeks or more, are accompanied by an increase in the direct bilirubin level, or are accompanied by clinical symptoms of liver injury or evidence of hepatic decompensation.³⁰ No similar effects have been seen with romiplostim.

In a study of extended romiplostim treatment involving 291 patients, 25 venous or arterial thromboembolic events occurred in 17 patients.^{18,31} In an eltrombopag extension study involving 299 patients, 16 patients had 21 thromboembolic events.²¹ The frequency of thromboembolic events did not increase with the duration of treatment in either study.^{18,21,31,32} Most thromboembolic events that have been associated with the use of thrombopoietin-receptor agonists have been observed in patients with at least one additional risk factor for thrombosis.

Bone marrow fibrosis may occur with use of either romiplostim or eltrombopag. In a study of extended use of eltrombopag in 83 patients, bone marrow–biopsy samples obtained after 12 and 24 months of treatment showed collagen fibrosis in 3 patients and a lesser degree of excess reticulin deposition in 30 patients.^{33,34} The increase in the level bone marrow reticulin appears to be reversible when treatment is discontinued.

AREAS OF UNCERTAINTY

There are no effective tools to predict bleeding risk in patients with immune thrombocytopenia. Some patients may have severe thrombocytopenia (platelet count, <10,000 per cubic millimeter) and no bleeding, whereas other patients may have recurrent hemorrhage at substantially higher counts. Because platelet counts do not accurately predict the bleeding risk, a major point of uncertainty in the management of immune thrombocytopenia is deciding when to start treatment, particularly in patients who have severe thrombocytopenia without bleeding symptoms.

With both romiplostim and eltrombopag, continuous use is required to maintain an increased platelet count. Therefore, treatment is usually prescribed with the expectation of an indefinite treatment duration. It has been suggested that intermittent use of thrombopoietin-receptor agonists (e.g., around the time of anticipated bleeding risk, such as surgery, participation in sporting events, or severe menorrhagia) may be appropriate for some patients; however, the efficacy and safety of this approach have not been established.³⁵ One report has indicated that repeated, intermittent administration of eltrombopag may be effective.³⁶ Thrombopoietin-receptor agonists do not have a role in the emergency treatment of bleeding because of their delayed onset of action.

The place of thrombopoietin-receptor agonists among second-line treatments of immune thrombocytopenia remains uncertain. Historically, splenectomy is the preferred second-line therapy for adults. Splenectomy is the only treatment associated with substantial rates of long-term remission²³ but carries the risk of perioperative death and complications and the long-term risk of infection.³⁷ Medical approaches to second-line treatment all have side effects, and high-quality evidence in support of their use is lacking.^{23,38} A recent evidence-based review was unable to make specific recommendations about the sequence of second-line therapies.²³

Appropriate management is also unclear for patients who have exhausted all second-line treatments (including splenectomy, rituximab, and other immunosuppressive drugs) and who do not have a response to thrombopoietin-receptor agonists. Such failure in response should call the diagnosis of immune thrombocytopenia into question; other conditions that may mimic this condition should be reconsidered (e.g., primary bone marrow failure syndromes and congenital platelet disorders). Whether different doses or frequencies of administration of thrombopoietin-receptor agonists might be beneficial in such patients is unknown.

Although patients who are receiving thrombopoietin-receptor agonists are required to enroll in registries as a condition of access to the medication only in the United States, careful monitoring before, during, and after the use of such drugs is recommended for all patients, given the potential for unanticipated toxic effects. The Intercontinental Cooperative ITP (Immune Thrombocy-

topenic Purpura) Study Group (ICIS) has more than 6000 prospectively registered patients. The ICIS Pediatric and Adult Registry on Chronic ITP has been amended to include questions related to treatment with thrombopoietin-receptor agonists (see www.itpbasel.ch).

The major clinical trials of thrombopoietin-receptor agonists have enrolled only patients with primary immune thrombocytopenia. Although it is reasonable to anticipate that these agents may be effective in secondary immune thrombocytopenia, this question has not been specifically tested. In many cases, the immune thrombocytopenia of other disorders (e.g., lupus erythematosus) responds to treatment of the underlying condition.³⁹

Little or no data are available to support the use of thrombopoietin-receptor agonists in either children or adolescents, including optimal doses and frequency of administration. It is important to note that the majority of children with immune thrombocytopenia will have a complete and spontaneous recovery.⁴⁰

GUIDELINES

The American Society of Hematology published an evidence-based guideline for the management of immune thrombocytopenia in 1996, before the development of thrombopoietin-receptor agonists.⁴¹ The society's guideline was revised in 2011.²³ In the revised recommendation, the use of thrombopoietin-receptor agonists was recommended for adult patients at risk for bleeding who have a relapse after splenectomy or who have a contraindication to splenectomy and do not have a response to at least one other therapy. It was also suggested that these agents could be considered for adult patients at risk for bleeding who have not had a response to one line of therapy and have not undergone splenectomy. A 2010 international consensus report recommended the use of thrombopoietin-receptor agonists as a treatment option for adult patients as second-line therapy and also as an option for adult patients in whom first-line and other second-line therapies have failed.³⁸ Neither guideline recommended the use of thrombopoietin-receptor agonists in children.

RECOMMENDATIONS

The patient described in the vignette has had chronic immune thrombocytopenia for more than

10 years. She has had relapses after both first- and second-line therapy. If she can afford the cost of long-term thrombopoietin-receptor agonist therapy (or if her insurer will provide coverage for such therapy), we would recommend continuing this treatment, with periodic bone marrow examination to monitor for evidence of bone marrow fibrosis and with assessment of her risk for thrombosis. The smallest dose that is required to maintain a platelet count of more than 50,000 per cubic millimeter should be used. However, given the unknown long-term risk of this therapy and its cost, the use of intermittent therapy at the time of her menstrual period might be considered. It should be emphasized to the patient that this choice is supported by very limited evidence. She should be counseled to use effective contraception because of the risk

of thrombopoietin-receptor agonists to the fetus. Pregnancy should be planned in consultation with an expert in the management of immune thrombocytopenia. If severe bleeding occurs, she should promptly seek medical attention; the patient should be advised that thrombopoietin-receptor agonists are not an effective short-term therapy for a bleeding episode.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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