

# Romiplostim for treating thrombocytopenia in chronic idiopathic thrombocytopenic purpura (ITP)

*First-in-class thrombopoietin receptor agonist stimulates platelet production, expanding the therapeutic options for treating patients with chronic ITP.*

## What's new, what's important

Romiplostim (Nplate) was approved by the US Food and Drug Administration in August 2008 for the treatment of chronic idiopathic thrombocytopenic purpura (ITP) refractory to corticosteroids, immunoglobulins, or splenectomy. It belongs to a novel class of thrombopoietin receptor agonists that stimulates bone marrow megakaryocytes to increase platelet production. This is an exciting treatment option for patients with chronic ITP.

The initial dose of romiplostim is 1 µg/kg once weekly, given as a subcutaneous injection. This dose may be titrated in increments of 1 µg/kg to achieve a platelet count  $\geq 50 \times 10^9/L$ ; the recommended maximum weekly dose is 10 µg/kg. Romiplostim should be prescribed by a healthcare provider who is enrolled in the Nplate NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program.

In general, romiplostim is well tolerated, but patients should be monitored for rare side effects, such as bone marrow fibrosis and reticulon formation.

— Jame Abraham, MD  
Section Editor

**R**omiplostim (Nplate, formerly AMG 531) is a thrombopoietin receptor agonist that stimulates platelet production by bone marrow megakaryocytes. The US Food and Drug Administration (FDA) has recently approved romiplostim for the treatment of thrombocytopenia in patients with chronic idiopathic thrombocytopenic purpura (ITP) who responded insufficiently to corticosteroids, immunoglobulins, or splenectomy.

Approval of romiplostim was based primarily on the results of two randomized, double-blinded, phase III trials, reviewed below.<sup>1</sup> These controlled trials, along with earlier uncontrolled studies<sup>2</sup> and data from additional reports of patients treated with romiplostim, involved relatively few patients and raised some safety

concerns, chief among which are risks for bone marrow reticulon fiber formation during romiplostim therapy and worsened thrombocytopenia after treatment is discontinued.<sup>3</sup> Thus, for the present, romiplostim may be prescribed only by physicians enrolled in the Nplate NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program. Full prescribing information for romiplostim and details of the NEXUS restricted distribution program are available at the Nplate NEXUS Program Web site, [www.nplatenexus.com](http://www.nplatenexus.com).

## Clinical efficacy

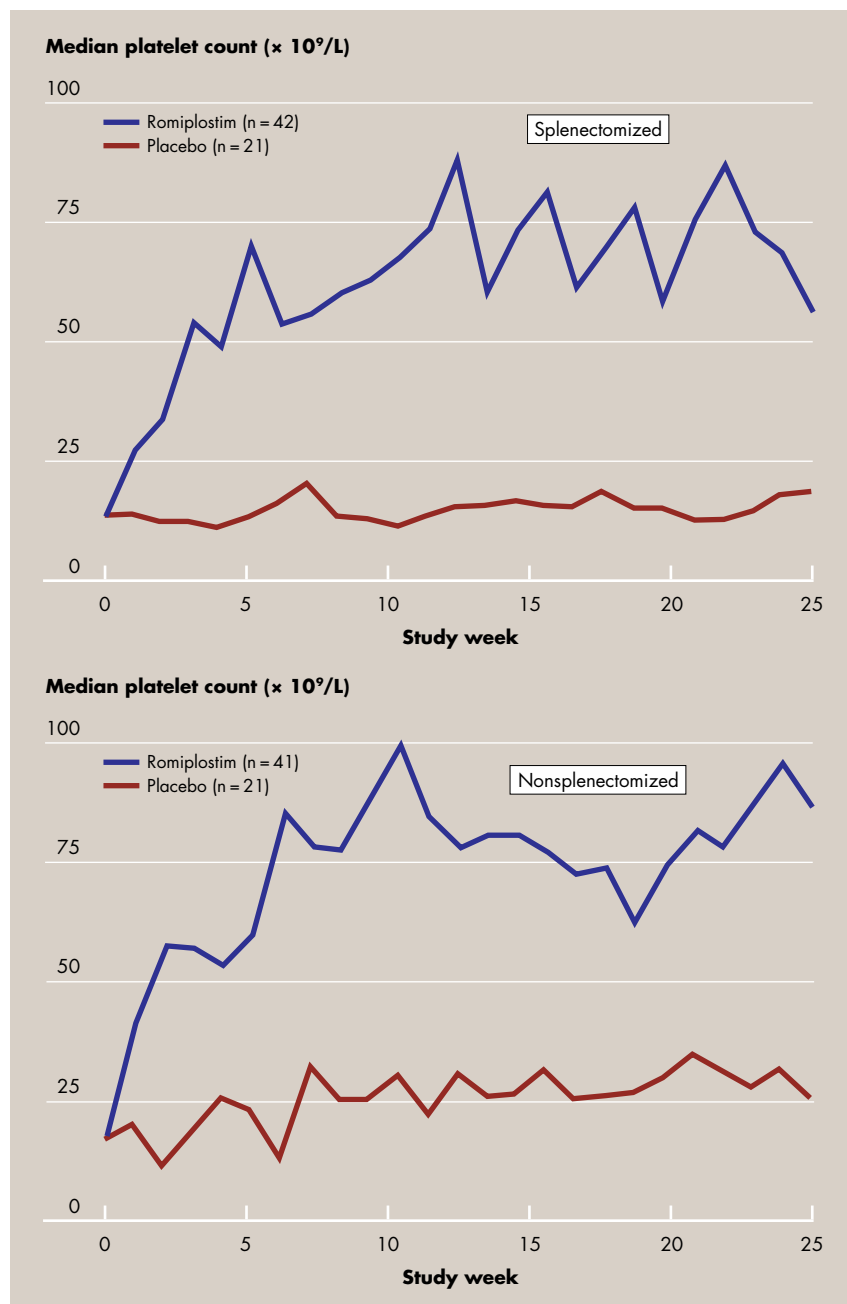
In two parallel phase III trials, 63 splenectomized and 62 nonsplenectomized patients with ITP (three platelet counts  $\leq 30 \times 10^9/L$ ) were randomized 2:1 to receive subcuta-

neous injections of romiplostim (n = 42 in the splenectomized study and n = 41 in the nonsplenectomized study) or placebo (n = 21 in each study) every week for 24 weeks.<sup>1</sup> The starting dose of study drug was 1 µg/kg, and doses were adjusted throughout the study to maintain a platelet count of  $50\text{--}200 \times 10^9/L$ .

Patients who were already receiving constant medical ITP treatment were allowed to continue on their current therapy. Rescue therapies (corticosteroids, intravenous immunoglobulin, platelet transfusions, anti-D immunoglobulin) were permitted to increase the platelet count in the case of bleeding or wet purpura or to prevent bleeding in patients at immediate risk for hemorrhage. A durable platelet response, defined as a platelet count  $\geq 50 \times 10^9/L$  during any 6 of the past 8 weeks of treatment, was the primary efficacy measure.

In the splenectomized groups (median platelet count =  $14 \times 10^9/L$  at baseline), a durable platelet response occurred in 16 (38%) of 42 romiplostim-treated patients and none of 21 patients receiving placebo ( $P = 0.0013$ ). In the nonsplenectomized groups (median platelet count =  $19 \times 10^9/L$  at study entry), a durable platelet response occurred in 25 (61%) of 41 romiplostim-treated patients and in 1 (5%) of 21 patients given placebo ( $P < 0.0001$ ). Overall platelet response, defined as a durable or transient response (four or more weekly

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**FIGURE 1** Median platelet counts in splenectomized (above) and nonsplenectomized (below) patients. Data include patients who received rescue medication. Adapted, with permission, from Kuter et al.<sup>1</sup>

platelet counts  $\geq 50 \times 10^9/L$  between weeks 2 and 25), occurred in 79% of the romiplostim-treated patients versus none of those receiving placebo in the splenectomized group ( $P < 0.0001$ ) and in 88% of romiplostim-treated patients versus 14% of those given placebo in the nonsplenectomized group

( $P < 0.0001$ ). For the combined studies, the rates were 83% for patients receiving romiplostim versus 7% for those given placebo ( $P < 0.0001$ ).

Median platelet counts over the 24-week course of the two studies are shown in Figure 1. In the splenectomized group, romiplostim-treated pa-

**TABLE 1**

Adverse events occurring in  $\geq 10\%$  of patients receiving romiplostim or placebo in two double-blind phase III trials<sup>a</sup>

Adverse event	Placebo (n = 41)	Romiplostim (n = 84)
Headache	32%	35%
Fatigue	29%	33%
Epistaxis	24%	32%
Arthralgia	20%	26%
Contusion	24%	25%
Petechiae	22%	17%
Diarrhea	15%	17%
Upper respiratory tract infection	12%	17%
Dizziness	0%	17%
Insomnia	7%	16%
Myalgia	2%	14%
Back pain	10%	13%
Nausea	10%	13%
Pain in extremity	5%	13%
Cough	17%	12%
Anxiety	12%	11%
Gingival bleeding	12%	11%
Abdominal pain	0%	11%
Nasopharyngitis	17%	8%
Ecchymosis	15%	7%

<sup>a</sup> Data from splenectomized and nonsplenectomized groups were pooled, since there were no significant differences between these groups. One nonsplenectomized patient randomly assigned to placebo received three doses of romiplostim in error and was included in the safety analysis as a patient given romiplostim.

Source: Kuter et al<sup>1</sup>

tients had a platelet response for an average of 12.3 weeks, compared with 0.2 weeks among those given placebo ( $P < 0.0001$ ). In the nonsplenectomized group, patients treated with romiplostim exhibited a platelet response an average of 15.2 weeks, versus 1.3 weeks among those who received placebo ( $P < 0.0001$ ). With data from the two studies combined, the mean number of weeks patients who received romiplostim had a platelet response was 13.8 weeks, compared with 0.8 weeks among those given placebo ( $P < 0.0001$ ).

Overall, rescue therapy was needed by 22% of romiplostim-treated patients

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# Finding a place for thrombopoietin receptor agonists in the treatment of chronic ITP

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**T**he term “paradigm shift” is frequently used in the medical literature. Perhaps nowhere is it more appropriate than to describe the use of thrombopoietin receptor (TPO-R) agonists in the treatment of chronic idiopathic thrombocytopenic purpura (ITP). The remarkable efficacy of romiplostim (Nplate, formerly AMG 531) and other TPO-R agonists highlights the role impaired platelet production plays in the pathogenesis of chronic ITP and challenges the traditional view of ITP as predominantly a disease of increased platelet destruction.<sup>1,2</sup>

TPO-R agonists include various agents that stimulate thrombopoiesis by binding to the TPO-R. Romiplostim is a peptibody that bears no sequence homology with TPO, a structure that avoids the problem of antibody response against endogenous TPO. Among other TPO-R agonists, eltrombopag (Promacta) is an oral nonpeptide small molecule that is similar in efficacy to romiplostim<sup>2</sup> and was just approved in the United States. Other TPO-R agonists will undoubtedly follow and provide clinicians and patients with a variety of treatment options, a welcome scenario in chronic ITP therapy.

## Defining a role for these agents

Although there is no question that TPO-R agonists are currently the most efficacious agents in treating chronic ITP, finding the proper place for these agents in the treatment

scheme of an individual patient with ITP could be challenging. Romiplostim or other TPO-R agonists are clearly the treatment of choice in patients who have failed to respond to splenectomy and are refractory to various other ITP treatments. Romiplostim can provide a clinically beneficial platelet count elevation in the majority of such patients, thereby reducing the risk of bleeding and allowing many patients to reduce or discontinue concomitant ITP treatments, as well as reduce their need for rescue immunoglobulin therapy.<sup>1</sup>

What is less clear is when romiplostim or another TPO-R agonist should be used in patients who have a recent diagnosis of ITP. Corticosteroids should still be the initial therapy, since a small percentage of adult patients will have a durable platelet response to steroids and may not need additional therapy. If steroids cannot be tapered off in 4–6 weeks, TPO-R agonists could be used at this point to achieve a platelet response that will allow most patients to be tapered off corticosteroid therapy, thereby avoiding the side effects of long-term corticosteroid use. However, it must be realized that TPO-R agonists are not disease-modifying agents; therefore, consideration should still be given to therapies that can achieve durable remissions.

Although splenectomy is potentially curative and has a response rate of around 60%, the inability to identify responders prior to the procedure is a drawback. Hence, with the availability

of TPO-R agonists, it can be expected that many physicians and patients would defer splenectomy, hoping for a spontaneous remission to occur while the patient is on these agents. Rituximab (Rituxan) is another relatively nontoxic therapy that can be tried while the patient is receiving romiplostim, although responses lasting over 1 year occur in only about 15% of patients.<sup>3</sup>

## Are the potential side effects worrisome?

To date, the side-effect profile of romiplostim has been extremely favorable, especially when compared with agents previously used for refractory ITP. However, it must be noted that only about 200 patients have been treated in clinical trials to date, with the longest treatment duration being about 3 years.<sup>4</sup> Therefore, the long-term side-effect profile of this novel agent will be evident only when larger numbers of patients are treated for much longer periods, especially with regard to the three side effects of major concern (bone marrow reticulin fibrosis, thrombotic events, and development of myeloid malignancies).

The formation and deposition of reticulin fibers in the bone marrow, although rare at the doses of romiplostim currently recommended, should be suspected if there is a loss of platelet response or development of other cytopenias or peripheral blood abnormalities such as leukoerythroblastosis. Limited experience suggests that the fibrosis and its sequelae are

reversible upon stoppage of the drug.

Despite romiplostim's potential to induce thrombocytosis, thrombotic events fortunately are rare with this agent and have occurred in patients with preexisting vascular disease. Therefore, it is prudent to avoid the use of romiplostim in such patients.

Due to the existence of TPO receptors in leukemic stem cells, induction of myeloid malignancies is a theoretical concern.

Although most patients will achieve a stable platelet count with romiplostim, marked fluctuations in platelet counts may be seen in some patients; management of such patients can be complicated and require frequent adjustment of the dosing schedule.

### When to discontinue therapy

The natural history of chronic adult ITP is characterized by gradual abatement of disease severity, and spontaneous remissions may occur in around 10% of patients.<sup>5</sup> Occasional patients

in the pivotal clinical trials of romiplostim continued to exhibit platelet counts  $\geq 50 \times 10^9/L$  after the drug was discontinued at the completion of the study. In my opinion, it would be reasonable to stop romiplostim after a year of treatment and monitor the platelet count to see whether a spontaneous remission has occurred. Rebound thrombocytopenia (platelet counts below baseline upon stoppage of the drug) is a concern and may require tapering of the drug.

Finally, the availability of TPO-R agonists would hopefully not lessen the rigor with which hematologists establish a diagnosis of ITP, as well as search for secondary causes such as hepatitis C or *Helicobacter pylori* infection. In the latter case, eradication of the infection can lead to durable responses.<sup>6</sup> Although TPO-R agonists could be effective in a variety of thrombocytopenic conditions, their use should be limited to approved indications until additional studies are completed and the drug's

side-effect profile in these conditions is determined.

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*From the Administrator's Perspective*

## Romiplostim: the risk evaluation and mitigation strategy (REMS)

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**H**ematopoietic growth factors that manage anemia and leukopenia have been available for many years. However, the development of agents that manage thrombocytopenia in a similar fashion has been less successful. Following the identification and isolation of thrombopoietin (TPO) and the thrombopoietin receptor c-Mpl in 1994, efforts to develop agents that stimulate

platelet production intensified. Two agents, recombinant human thrombopoietin (rHuTPO) and recombinant human megakaryocyte growth and differentiation factor (rHuMGDF), underwent study in a multitude of settings. Although initially promising, the development of these agents was halted in 1998 after the emergence of neutralizing antibodies that cross-reacted with endogenous TPO, producing thrombocytopenia

in healthy subjects.<sup>1</sup>

Ten years later, the US Food and Drug Administration (FDA) approved romiplostim (Nplate, formerly AMG 531) for the treatment of chronic idiopathic thrombocytopenic purpura (ITP) in patients with an inadequate response to conventional ITP therapy with corticosteroids, intravenous immunoglobulin, or splenectomy. Romiplostim is a TPO-mimetic peptide consisting

of a peptide domain that binds to and stimulates the TPO receptor, coupled with an Fc carrier domain. The peptide domain bears no sequence homology to TPO and is unlikely to stimulate the production of neutralizing antibodies to endogenous TPO.

### Safety concerns

Efficacy data and a description of serious adverse effects related to romiplostim are reviewed in the research summary portion of this month's Community Translations. Small study size, the potential for serious adverse effects, and recent data suggesting increased mortality with the use of erythropoiesis-stimulating agents in some types of cancer have given clinicians and the FDA cause for concern. As a result, the FDA has required Amgen to establish a risk evaluation and mitigation strategy (REMS) for romiplostim. The intent of a REMS program is to manage known or potential serious risks associated with a drug or biological product—and to ensure the product's benefits outweigh its risks. The FDA was granted the power to require REMS for any drug or biologic product in the FDA Amendments Act of 2007.<sup>2</sup> The requirements for individual REMS programs are product specific and may involve education strategies, certification/registration of prescribers and pharmacists, restricted distribution, specific patient monitoring requirements, or any combination of these elements that are deemed necessary to ensure safe use of a drug or biological agent.

### Paperwork requirements

The Nplate NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) Program fulfills the REMS requirement that has been instituted for romiplostim. To prescribe and use the drug, physicians and their institutions must undergo a one-time registration with the program. The registration form serves as acknowledgment that prescribers understand the appropriate use, dosing,

monitoring, risks, and patient education requirements of romiplostim. Patients must also be registered and provide consent for disclosure of health information to the Nplate NEXUS Program. The patient registration form also serves as an acknowledgment that patients have been provided with a medication guide and understand the risks involved with receiving romiplostim. A baseline patient data form pertaining to the individual's ITP history must be completed and faxed to the Nplate NEXUS Program. A safety questionnaire also must be submitted twice a year for each patient who is receiving romiplostim. Upon discontinuation of romiplostim, a follow-up form must be completed when the drug is stopped and again 6 months later. Adverse events must be reported to the Nplate NEXUS Program or the FDA's MedWatch. Romiplostim is available to registered physicians/institutions on a patient-specific basis through wholesaler channels. A small additional stock may be kept on hand to prevent delays when initiating romiplostim therapy in new patients.

### Expense

Not surprisingly, the cost of romiplostim is high and must be taken into account when considering a patient for treatment. The wholesale acquisition cost of a single-use vial of romiplostim is \$1,062.50 for a 250-

µg vial and \$2,125.00 for a 500-µg vial. Even with insurance coverage, patients may be required to absorb a significant cost burden. A reimbursement assistance program is available through NEXUS to verify coverage, assist with claims, and seek alternative funding options for patients.

Development of TPO receptor agonists continues at a rapid pace. Current studies of romiplostim are examining its use in myelodysplastic syndrome and as platelet support in patients receiving chemotherapy. Other TPO-mimetics, such as the oral small molecule eltrombopag (Promacta), have either been recently approved or are in clinical development. Like romiplostim, these agents are likely to be expensive and involve similar risk-mitigation strategies. The availability of viable TPO-mimetic agents represents an exciting advancement. However, safety concerns, prohibitive cost, and increased paperwork requirements may initially hinder their rate of adoption into routine clinical practice.

### References

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versus 60% of patients receiving placebo ( $P < 0.0001$ ). Of patients receiving concurrent ITP therapy at the start of treatment, 20 (87%) of 23 patients receiving romiplostim reduced or discontinued such treatment, compared with 6 (38%) of 16 receiving placebo.

Most of the patients achieving a durable response did so at a relatively stable dose of the study drug ( $\pm 1$  µg/kg variance) during the past 8 weeks, although there was a wide range of stable doses (1-7 µg/kg) among individual patients. Overall, the median

doses needed to maintain the platelet count within the target range ( $50-200 \times 10^9/L$ ) were approximately 3 µg/kg in splenectomized patients and 2 µg/kg in nonsplenectomized patients.

On multivariate analysis, the only factors significantly associated with a durable response were baseline weight  $< 70$  kg ( $P = 0.0106$ ) and no splenectomy ( $P = 0.0306$ ). After completion of the placebo-controlled studies, 100 patients whose platelet count subsequently decreased to  $50 \times 10^9/L$  or below entered an open-label extension study of

long-term romiplostim therapy, with the majority maintaining platelet counts  $\geq 50 \times 10^9/L$  throughout the study (median duration of treatment, 60 weeks; maximum duration, 96 weeks).<sup>3</sup>

## Adverse events

The most common adverse events in the two phase III trials are shown in Table 1; among those that occurred more frequently with romiplostim than with placebo were dizziness (17%), insomnia (16%), myalgia (14%), abdominal pain (11%), and pain in the extremities (13%). Nine patients reported a serious bleeding event, including five (6%) receiving romiplostim and four (10%) given placebo. Overall, grade  $\geq 2$  bleeding events occurred in 15% of patients treated with romiplostim and 34% of those receiving placebo. Two patients receiving placebo died: one from a cerebral hemorrhage and one from a pulmonary embolism. One romiplostim-treated patient died from an

intracranial hemorrhage after starting aspirin to treat thrombosis and then discontinuing romiplostim. One romiplostim nonresponder with increased bone marrow reticulin had an additional increase in reticulin that returned to normal 3 months after stopping drug treatment. One romiplostim patient with a history of peripheral vascular disease had popliteal artery thrombosis. No antibodies to romiplostim or thrombopoietin were detected in either controlled study.

Earlier studies of romiplostim in chronic ITP<sup>2</sup> and additional experience included reports of thrombotic events and worsening thrombocytopenia after stopping romiplostim. Overall, 271 patients with chronic ITP have been exposed to romiplostim.<sup>3</sup> As noted, the major safety concerns identified by the FDA were risk for marrow reticulin formation and worsened thrombocytopenia after drug discontinuation; other potential risks include marrow fibrosis

during long-term therapy and thrombosis due to an excessive increase in platelet count.

The recommended initial dose of romiplostim is 1  $\mu\text{g}/\text{kg}$  subcutaneously once weekly, with adjustment to achieve a platelet count  $\geq 50 \times 10^9/L$  as necessary to reduce bleeding risk. Romiplostim must be administered weekly by a healthcare provider. It should not be used in an attempt to normalize platelet counts.

## References

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