New Drug

Romiplostim in Chronic Immune Thrombocytopenic Purpura

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ABSTRACT

Background: Immune thrombocytopenic purpura (ITP) is characterized by platelet deficiency due to platelet destruction and/or inadequate production. Initial therapy consists of corticosteroids or intravenous immunoglobulin (IVIg). Patients with chronic refractory disease might undergo splenectomy. Although there is no treatment of choice in those who do not respond to splenectomy, immunosuppressive agents are typically prescribed. Romiplostim is the first available drug in a recently developed class of agents that work through stimulation of the thrombopoietin (TPO) receptor (c-Mpl) to increase platelet production.

Objective: The aim of this report was to review the mechanism of action, pharmacology, clinical activity, and adverse events associated with the use of romiplostim for the treatment of thrombocytopenia in patients with chronic ITP.

Methods: MEDLINE, Google Scholar, International Pharmaceutical Abstracts, and Web of Science were searched for English-only clinical trials and reviews (publication dates: 2000–June 1, 2009; key terms: *romiplostim, Nplate, ITP,* and *idiopathic and immune thrombocytopenic purpura*). Abstracts from the 2000–2008 meetings of the American Society of Hematology and references from relevant articles were reviewed.

Results: A total of 6 studies were included. Romiplostim is the first marketed agent developed to directly stimulate the bone marrow to produce platelets. Produced in *Escherichia coli* using recombinant DNA technology, it is an Fc-peptide fusion protein. It works intracellularly in a manner similar to that of the naturally occurring TPO to activate the transcriptional pathways, leading to increased platelet production via stimulation of the c-Mpl receptor. Romiplostim was approved by the US Food and Drug Administration for the treatment of chronic ITP primarily based on the findings from 2 multicenter, randomized, placebo-controlled, parallel-group studies in 125 adult patients with chronic ITP and an insufficient response to corticosteroids, IVIg, and/or splenectomy. The most common prior treatments were corticosteroids (94%) and IVIg (80%). Sixty-three patients (50%) were splenectomized a median of 6.6 years earlier. Baseline platelet counts were $<30 \times 10^9$ cells/L. The initial dose of romiplostim was 1 μg/kg/wk SC, with adjustments to maintain platelet counts between 50 and 200×10^9 cells/L. The primary end point was a durable platelet response ($\geq 50 \times 10^9$ cells/L for ≥6 of the last 8 weeks of treatment). The proportion of patients in whom a durable platelet response was achieved was significantly greater with romiplostim than with placebo (49% vs 2%, respectively; $P < 0.001$). Overall platelet responses (durable plus transient) were achieved in 83% (69/83) with romiplostim and 7% (3/42) with placebo ($P < 0.001$). An interim report of findings from an ongoing extension study found that response was maintained for up to 156 weeks (median, 69 weeks) with romiplostim. The most common adverse events were headache (37%), nasopharyngitis (32%), contusion (30%), epistaxis (30%), fatigue (30%), arthralgia (25%), and diarrhea (25%).

Conclusions: Based on the findings from this review, romiplostim administration has been associated with a durable platelet response in these patients with refractory chronic ITP. Romiplostim has been found to be generally well tolerated. (*Clin Ther.* 2009;31: 1887–1907) © 2009 Excerpta Medica Inc.

Key words: immune (idiopathic) thrombocytopenic purpura, ITP, Nplate, romiplostim.

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INTRODUCTION

Immune (idiopathic) thrombocytopenic purpura (ITP), also known as immune thrombocytopenia,[1] is characterized by a platelet deficiency caused by platelet destruction and/or inadequate thrombopoiesis. The disorder may be classified according to age (adult or pediatric) and/or by the duration of thrombocytopenia (acute or chronic).[2] Children might develop an acute type that follows an acute viral illness or immunization. Acute ITP is usually self-limiting and, in 70% to 80% of patients, resolves without treatment within 6 months of onset.[3,4] The adult type is typically chronic and has not been associated with any predisposing illness; ~5% of patients may recover spontaneously.[5] An international working group recently recommended that the use of the word *acute* be discontinued and suggested the term *newly diagnosed ITP* for all cases at diagnosis.[1] They also suggested the terms *persistent* for cases lasting 3 to 12 months and *chronic* for those with ITP lasting >12 months.[1] However, because these recommendations are new, they were not applied in any of the studies reviewed here.

Incidence of ITP

Based on findings from European studies, the incidence of *ITP in adults,* defined as a platelet count ≤50 × 10^9 cells/L, was 1.6 to 2.25 cases per 100,000 population per year.[6,7] The median age at diagnosis was 56 years. In those aged ≥60 years, the incidences in men and women were similar. In adults aged <60 years, the disorder is much more common in women than in men (female:male ratio, 3:1).[6–8] Few data are available concerning the potential effects of race or ethnicity on the disorder. A literature review that analyzed census-based data from 561 patients with ITP reported that the disorder was less common than expected.[9] The proportion of black patients with ITP in the United States was lower than the proportion of black people in the population.[9] However, an analysis of data from 4,762,505 US veterans found that the difference in the prevalences of ITP in white and black men in the United States were 176.4 and 189.3 per 100,000 population, respectively.[10] In an Italian study, Stasi et al[11] reported that in a group of 87 adults with platelet counts ≥50 × 10^9 cells/L, who went untreated for ≥6 months, the prevalence of spontaneous resolution of chronic ITP was 9%.

Etiology of ITP

Although the exact cause of ITP is unknown, specific immune characteristics have been identified in patients with ITP. Platelets may be destroyed by antiplatelet antibodies directed at platelet glycoproteins IIb/IIIa and IB/IX.[12,13] These antibodies bind to the platelets, which are then phagocytized by macrophages, predominantly within the spleen, liver, and bone marrow.[14,15] However, in up to half of patients with ITP, autoantibodies are undetectable.[13,16] A direct cytotoxic effect of T cells on platelet destruction has been proposed based on in vitro data[17] but has not been confirmed clinically.[18] A detailed review of the pathophysiology of ITP is available elsewhere.[15]

Presentation of ITP

Patients may be symptomatic or asymptomatic at diagnosis. In a report from an international working group on the standardization of terminology, definitions, and outcome criteria in ITP, adult ITP was subclassified as primary or secondary.[1] *Primary ITP* was defined as an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count, <100 × 10^9 cells/L) in the absence of other causes or disorders that might be associated with thrombocytopenia. *Secondary ITP* was defined as all other types of immune-mediated thrombocytopenia. The working group described 4 phases of ITP: (1) newly diagnosed (onset within 3 months of diagnosis); (2) persistent (duration, 3–12 months; includes disease that has not achieved spontaneous remission and/or has not maintained complete remission without treatment); (3) chronic (duration, >12 months); and (4) severe (bleeding symptoms at presentation sufficient to require treatment, or the occurrence of new bleeding symptoms that require additional treatment with a different platelet-enhancing agent or an increased dose of current treatment).

Management of ITP

The goal of ITP treatment is to prevent major bleeding episodes by maintaining an adequate platelet count in the blood. Treatment is indicated in patients whose severity of thrombocytopenia and clinical condition put them at an increased risk for bleeding. Although there is no clearly defined platelet count at which therapy should be initiated, the American Society of Hematology practice guideline[5] states that patients with a platelet count >50 × 10^9 cells/L who are asymptomatic or who have minor purpura do not routinely require treatment. The guideline states that withholding treatment in patients with a platelet

count <20 × 10^9 cells/L is inappropriate regardless of their present symptoms, and in patients with a platelet count <50 × 10^9 cells/L who present with significant mucous membrane bleeding or risk factors for bleeding, such as peptic ulcer disease, hypertension, or a vigorous lifestyle. The guideline considers it inappropriate to withhold treatment at the patient's request if the platelet count is <20 × 10^9 cells/L.[5] Additional risk factors that may influence treatment decisions include occupation, comorbidities such as cerebrovascular disease, concurrent medications (anticoagulants), and the need for surgery or other invasive procedures.[19] Patients with severely low platelet counts (<10 × 10^9 cells/L) are at risk for a major bleed and require treatment.[2,19]

First-Line Treatment

First-line treatment includes the administration of corticosteroids or intravenous immunoglobulin (IVIg). If the condition is not life-threatening, oral treatment with prednisone 1 to 2 mg/kg/d in a single dose or in divided doses might be employed. In up to two thirds of patients, complete or partial remission is achieved within 7 to 10 days with oral corticosteroid use.[20,21] The duration of treatment depends on the platelet response. Most remissions are short-lived, with relapse occurring when the corticosteroid dose is reduced.[21,22] Sustained remission occurs in 20% to 40% of patients.[5,8,19,23]

IVIg is typically used in patients who have not responded to corticosteroids, who have contraindications to corticosteroids, or who require a rapid increase in platelets (eg, those with severe or critical bleeding or before surgery).[20] The current standard dose is 1 mg/kg/d for 1 or 2 days.[20] Platelet counts may begin to increase in as little as 1 day and continue to increase through the first week after treatment initiation.[20,24] Platelet counts increase to ≥50 × 10^9 cells/L in as many as 80% of patients and ≥100 × 10^9 cells/L in up to 50% of patients.[25] Responses are transient, and platelet counts may begin to decline within 3 to 4 weeks after treatment initiation.[5,26]

Another first-line treatment is anti-D Ig, which is effective only in patients who are Rh+ and nonsplenectomized. Doses ranging from 50 to 80 μg/kg/d have been associated with increased platelet counts within 48 to 72 hours of treatment initiation.[20,27] A response rate of 70%, beginning 72 hours after administration, was reported in a single-arm clinical trial in 272 patients (137 adults) with ITP and a *need for treatment,* which the authors defined as a platelet count that was "usually" <30 × 10^9 cells/L. Anti-D was administered at a dose of 25 μg/kg/d for 4 or 5 days or as a single infusion.[27,28] The duration of response was >21 days in 50% of the responders. In a prospective, randomized study in 27 nonsplenectomized patients with acute ITP and a platelet count ≤30 × 10^9 cells/L, the administration of a higher dose (75 μg/kg/d) was associated with a faster and more durable response.[29] The median platelet count on the day after the first dose was 43 × 10^9 versus 7.5 × 10^9 cells/L in patients who received 75 μg/kg versus those who received 50 μg/kg, respectively (P = 0.012). On day 7, the median platelet counts among patients who received 75 and 50 μg/kg were 153 and 64.5 × 10^9 cells/L (P = 0.001). The median duration of the response was 46 days among those who received 75 μg/kg and 21 days among those who received 50 μg/kg (P = 0.03).

Second-Line Treatment

Patients who do not respond to first-line treatment with corticosteroids or IVIg may be candidates for splenectomy.[5,8] In general, splenectomy is recommended in patients whose duration of ITP is ≥6 weeks and who have severe thrombocytopenia (platelet count, <10 × 10^9 cells/L) with no bleeding symptoms, and in patients whose duration of ITP is ≥3 months, who have had a transient or incomplete response to primary therapy, and who have a platelet count of 10 to 30 × 10^9 cells/L.[5] A large review involving 2623 patients[30] reported a rate of complete response (defined as a platelet count of >150 × 10^9 cells/L) of 66% after splenectomy. In 14 case series of adults, 456 of 707 patients (64.5%) who underwent splenectomy had a complete response with a median follow-up of 7.25 years.[30]

Approximately 25% to 30% of patients with chronic ITP do not respond to initial treatment or splenectomy.[2,19] Several immunosuppressive agents have been used for the management of ITP in these patients, including azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, and rituximab.[19,31] Other agents (danazol, vinca alkaloids) work through the inhibition of platelet clearance.[19] In a review of 90 studies of the management of adults with chronic ITP that persists after splenectomy and a baseline platelet count <30 × 10^9 cells/L, rates of response to immunosuppressives (azathioprine, cyclophosphamide,

cyclosporine, danazol, mycophenolate mofetil, rituximab, and vinca alkaloids) ranged from 56% to 96%. The majority of responses with each drug, with the exception of cyclophosphamide, were partial (>30 × 10^9 cells/L).[32] However, few patients received each drug (azathioprine, 53 patients; rituximab, 35; vinca alkaloids, 34; cyclophosphamide, 28; cyclosporine, 8; mycophenolate mofetil, 7; and danazol, 52), and information on concurrent medications was available from only 27% of patients from whom individual data were available. The authors concluded that evidence of the effectiveness of any immunosuppressive treatment of ITP and persistent thrombocytopenia after splenectomy was minimal and that further studies were needed to determine effectiveness and tolerability.

The objective of this report was to review the mechanism of action, pharmacology, pharmacokinetic and pharmacodynamic properties, clinical data, and adverse events associated with use of the thrombopoietic agent romiplostim for the management of chronic ITP in adults.

MATERIALS AND METHODS

MEDLINE, Google Scholar, International Pharmaceutical Abstracts, and Web of Science were searched for English-only clinical trials and therapeutic reviews (publication dates: 2000–June 1, 2009; key terms: *romiplostim, Nplate, ITP,* and *idiopathic and immune thrombocytopenic purpura*). Abstracts from the 2000–2008 meetings of the American Society of Hematology and references from relevant articles were reviewed.

RESULTS

A total of 6 studies were identified and included in this review.

Indications

Romiplostim* is the first available drug in a recently developed class of agents, the thrombopoietics. It was approved by the US Food and Drug Administration (FDA) in 2008 for the treatment of thrombocytopenia in patients with chronic ITP and a history of insufficient response to corticosteroids, immunoglobulins or splenectomy. The product labeling indicates that it should be used only in patients with ITP whose thrombocytopenia and clinical condition increase the risk for bleeding.[33] The manufacturer recommends using the lowest dose of romiplostim that will achieve and maintain a platelet count ≥50 × 10^9 cells/L as necessary to reduce the risk for bleeding, and that it should not be used in an attempt to normalize platelet counts.[33]

*Trademark: Nplate® (Amgen Inc., Thousand Oaks, California).

Mechanism of Action

Romiplostim is an Fc-peptide fusion protein, or peptibody. Peptibodies are engineered molecules that bind to human drug targets. Peptibodies contain peptides linked to constant domains of antibodies. Romiplostim consists of 2 identical single-chain subunits, each containing human IgG1 Fc domains linked covalently at the C-terminus to a peptide that contains 2 thrombopoietin (TPO) receptor (c-Mpl)–binding domains, for a total of 4 binding sites. It works intracellularly in a manner similar to that of the naturally occurring TPO—that is, it activates the transcriptional pathways that stimulate the c-Mpl receptor, leading to increased platelet production. Romiplostim is produced in *Escherichia coli* by recombinant DNA technology and was designed to directly stimulate the bone marrow to produce platelets.[33]

Pharmacokinetics and Pharmacodynamics

Romiplostim is administered by subcutaneous injection. Weekly administration at doses of 3 to 15 μg/kg has been associated with a median T_{max} of 14 hours (range, 7–50 hours) and a median $t_{1/2}$ of 3.5 days (range, 1–34 days).[33] Although no correlation has been found between dose and serum drug concentrations, increases in platelet counts might be dose dependent.[34,35] After a single subcutaneous dose of romiplostim 1 to 10 μg/kg in patients with ITP, peak platelet counts were 1.3- to 14.9-fold greater than baseline over a period of 2 to 3 weeks after administration (**Table I**).[33]

Two Phase I, randomized, placebo-controlled, dose-escalation studies assessed the pharmacokinetic and pharmacodynamic properties of romiplostim in healthy volunteers (**Table II**).[34,35] In the first study, romiplostim 0.3 to 10 μg/kg IV (n = 12) or 0.1 to 2 μg/kg SC (n = 20) was administered as a single dose.[34] In the second trial, 30 subjects were randomly assigned to receive a single dose of romiplostim by the subcutaneous route at doses of 0.3 to 2 μg/kg (n = 24) or placebo (n = 6).[35] The mean baseline platelet counts were 227 and 230.6 × 10^9 cells/L in the first and second trials, respectively. With subcutaneous and intravenous administration, increases from baseline in platelet counts were compa-

Table I. Pharmacodynamic properties of romiplostim after subcutaneous administration.

Study (Design)/ Study Group	No. of Subjects	Mean Baseline Platelet Count, $\times 10^9$ cells/L	Mean Peak Platelet Count, $\times 10^9$ cells/L	No. (%) of Subjects With ≥1.5-Fold Increase in Platelet Count	No. (%) of Subjects With ≥2-Fold Increase in Platelet Count	Mean Peak, d
Wang et al[34] (Phase I, dose-finding study in healthy volunteers)						
Romiplostim 1 μg/kg	4	226	412	3 (75)	1 (25)	14*
Romiplostim 2 μg/kg	8	216	532	8 (100)	6 (75)	13*
Inactive vehicle (placebo)	16	231	265	0	0	15*
Kumagai et al[35] (Phase I, dose-finding study in healthy Japanese male volunteers)						
Romiplostim 0.3 μg/kg	8	228.4	260.8	0	0	10.38*
Romiplostim 1 μg/kg	8	230.4	402.0	4 (50)	1 (13)	12.75*
Romiplostim 2 μg/kg	8	233.1	465.5	7 (88)	3 (38)	13.25*
Inactive vehicle (placebo)	6	216.8	235.2	0	0	21.50*
Newland et al[36] (Phase I/II open-label study in patients with ITP)						
Romiplostim 30 μg on days 1 and 15†	4	10.8*	NR	NR	1 (25)	10.5
Romiplostim 100 μg on days 1 and 15†	4	14.6*	NR	NR	4 (100)	9.0
Romiplostim 300 μg on days 1 and 15†	7	15.5*	NR	NR	4 (57)	12.0
Romiplostim 500 μg on days 1 and 15†	1	28.8*	1062	NR	1 (100)	10.0
Bussel et al[37]						
Phase I (open-label, dose-escalation study in patients with ITP)						
Romiplostim 0.2–1 μg/kg	12	9*	NR	NR	1 (25)‡	NR
Romiplostim 3 μg/kg	4	12*	163	NR	2 (50)	11
Romiplostim 6 μg/kg	4	12*	309	NR	2 (50)	10
Romiplostim 10 μg/kg	4	12*	746	NR	3 (75)	14
Phase II (double-blind, placebo-controlled study in patients with ITP)						
Romiplostim 1 μg/kg	8	17	135	NR	7 (88)	18
Romiplostim 3 μg/kg	8	12	241	NR	3 (38)	19
Romiplostim 6 μg/kg	1	15	520	NR	1 (100)	NR
Inactive vehicle (placebo)	4	29	81	NR	1 (25)§	63

ITP = immune thrombocytopenic purpura; NR = not reported.

*Median.

† Treatment was also administered on day 22 if day-15 platelet count was >750 × 10^9 cells/L.

‡ This patient had received rituximab 4 weeks before enrollment in the study.

§ This patient experienced spontaneous remission after having undergone a splenectomy 3.5 months before entering the study.

Table II. Clinical studies of romiplostim in the management of immune thrombocytopenic purpura (ITP).

Study/Design/Study Group	No. of Subjects	Baseline Platelet Count, $\times 10^9$ cells/L	Response Rate, %	Time to Response	Adverse Events, %[a]
Wang et al[34] (Phase I, dose-finding study in healthy male volunteers; mean age, 31.5 y; 94% white)					Romiplostim/placebo: headache, 12.5/6, sore throat, 12.5/6, back pain, 3/19
Romiplostim 0.3–10 μg/kg IV	12	Mean, 214	NA	Peak range, 12–16 d	
Romiplostim 0.1–2.0 μg/kg SC	20	Range, 225–232	NA	Peak range, 12–16 d	
Inactive vehicle (placebo)	16	Mean, 231	NA	–	
Kumagai et al[35] (Phase I, dose-finding study in healthy Japanese male volunteers; mean age, 28.5 y)					Romiplostim/placebo: abdominal pain, 17/33; nasopharyngitis, 13/17; elevated aminotransferases, 13/17; diarrhea, 13/33; uric acid elevation, 8/0; feeling hot, 8/0; loose stool, 8/0; myalgia, 8/0; neck pain, 8/0; stomatitis, 8/0
Romiplostim 0.3–2.0 μg/kg SC	24	Range, 228–233	NA	Mean peak, 12 d at 1–2 μg/kg	
Inactive vehicle (placebo)	6	216.8	NA	–	

(continued)

Table II (continued).

Study/Design/Study Group	No. of Subjects	Baseline Platelet Count, $\times 10^9$ cells/L	Response Rate, %	Time to Response	Adverse Events, %[a]
Newland et al[36] (Phase I/II, open-label[b] study in adults with ITP; median age, 50 y, 63% female, 94% white, 6% black)					Headache, 50; arthralgia, 31; fatigue, contusion, epistaxis, petechiae, 25 each; ecchymosis, injection-site hemorrhage, peripheral edema, nasopharyngitis, 19 each; diarrhea, mouth hemorrhage, oral mucosal petechiae, back pain, musculoskeletal pain in extremity, hematoma, 13 each; breast mass (female), menorrhagia, 10 each
Romiplostim 30, 100, 300, or 500[c] µg SC on days 1 and 15 (day 22 if day-15 platelet count >50 $\times 10^9$ cells/L)	15	Median, 14.5	72[d,e]	Median peak, 10 d	
Bussel et al[37]					
Phase I (open-label, dose-escalation study in adults with ITP; median age, 45 y; 71% female; 92% white, 8% black)[f]					Contusion, 67; ecchymosis, 67; headache, 46
Romiplostim 0.2–10 µg/kg SC × 2	24	Range, 9–12	58.3[d]	Median range, 5–8 d	
Phase II (double-blind, placebo-controlled study in adults with ITP; median age, 49 y; 71% female; 67% white, 5% black, 28% other)[g]					Romiplostim/placebo: contusion/ecchymosis, 59/75; epistaxis, 41/50; headache, 29/0; oral blistering, 29/0[h]
Romiplostim 1, 3, 6 µg/kg/wk SC × 6	16	Range, 12–17	75[d]	By day 8 in 9 patients	
Inactive vehicle (placebo)	4	Range, 6–49	25[d]	–	

(continued)

Table II (continued).

Study/Design/Study Group	No. of Subjects	Baseline Platelet Count, $\times 10^9$ cells/L	Response Rate, %	Time to Response	Adverse Events, %[a]
Kuter et al[39] (double-blind, placebo-controlled study in adults with ITP; mean age, 52 y; 65% female; 82% white, 7% black, 6% Hispanic, 5% other)					Romiplostim/placebo: headache, 35/32; fatigue, 32/29; epistaxis, 32/24; arthralgia, 26/20; contusion, 25/24; petechiae, 17/22; diarrhea, 17/15; upper respiratory infection, 17/22; dizziness, 17/0; insomnia, 16/7; myalgia, 14/2; back pain, 13/10; nausea, 13/10; extremity pain, 13/5; cough, 12/17; anxiety, 11/12; gingival bleeding, 11/12; abdominal pain, 11/0; nasopharyngitis, 8/17; ecchymosis, 7/15
Splenectomized					
Romiplostim 1–2 μg/kg/wk, 2 μg/kg SC every 2 weeks	42	Mean, 14	38[i,j]	Mean, 13.8 wk	
Inactive vehicle (placebo)	21	Mean, 15	0	–	
Nonsplenectomized					
Romiplostim 1–2 μg/kg/wk, 2 μg/kg SC every 2 weeks	41	Mean, 19	61[k]	Mean, 15.2 wk	
Inactive vehicle (placebo)	21	Mean, 19	5	–	

[a]See text for serious adverse events.
[b]A total of 81% of patients were splenectomized.
[c]The 500-μg dose was discontinued in 1 patient due to excessive platelet count (>450 × 10^9 cells/L).
[d]*Response* defined as platelet count that was >2-fold baseline count and between 50 and 450 × 10^9 cells/L.
[e]At dose equivalents ≥1 μg/kg (n = 11).
[f]A total of 29% of patients were receiving steroids; 79% were splenectomized.
[g]A total of 23% of patients were receiving steroids; 76% were splenectomized.
[h]All patients with oral blistering had a history of oral bleeding and had bleeding at the time of enrollment.
[i]*Durable platelet response* defined as a platelet count ≥50 × 10^9 cells/L for ≥6 weeks during last 8 weeks of the 24-week period.
[j]$P = 0.001$.
[k]$P < 0.001$.

rable and dose related. Platelet counts began to increase within 1 to 3 days after intravenous administration and 4 to 9 days after subcutaneous administration. Peak platelet counts were achieved on days 11 to 15 after intravenous administration and days 8 to 20 (mean, 12–16 days) after subcutaneous administration.

A *biologically active dose* was defined as that which would produce a 2-fold increase in platelet counts over baseline in ≥2 subjects in a dosing cohort. After intravenous administration, a ≥1.5-fold increase in platelet count was achieved in 9 of 12 subjects (75%): 1 with the 0.3-μg/kg dose, and 4 each with the 1- and 10-μg/kg dose. A ≥2-fold increase in platelet count was achieved with the 1-μg/kg dose (2/4 subjects [50%]) and 10-μg/kg dose (4/4 subjects [100%]). After subcutaneous administration, there were no responses among the 8 subjects (4 per dose) who received the drug at a dose of 0.1 or 0.3 μg/kg. A platelet increase of ≥1.5-fold was achieved in 7 of 12 subjects (58.3%) who received the 1-μg/kg dose and in 15 of 16 subjects (93.8%) who received the 2-μg/kg dose. Increases ≥2-fold were found in 2 of 12 subjects (16.7%) who received 1 μg/kg and in 9 of 16 subjects (56.3%) who received 2 μg/kg. In 1 trial, platelet counts returned to baseline within 28 days of administration.[34] In the other, platelet count increases lasted 2 to 15 days with the 1-μg/kg dose and 6 to 16 days with the 2-μg/kg dose.[35]

The pharmacokinetics appeared to be nonlinear with the dose after intravenous administration. The central volume of distribution after the administration of an intravenous bolus injection decreased from 122 mL/kg to 78.8 and 48.2 mL/kg after the administration of intravenous doses of 0.3, 1.0, and 10 μg/kg, respectively. The reason for this decrease is unknown. The authors speculated that the binding of romiplostim to c-Mpl receptors might be nonlinear at the doses employed. Respective clearances were 754, 63.0, and 6.69 mL/kg/h, and $t_{1/2}$ values were 1.50, 2.41, and 13.8 hours after the administration of a single intravenous bolus at doses of 0.3, 1.0, and 10 μg/kg.[34]

After the administration of a single subcutaneous dose in healthy volunteers, most of the serum concentrations were below the lower limit of quantitation of the assay (18 pg/mL). Available data suggested that absorption appeared to be slow after the subcutaneous administration. The peak concentration after subcutaneous administration of 2 μg/kg was achieved within 24 to 36 hours. Bioavailability could not be determined based on the limited data available.[34] With weekly administration of subcutaneous romiplostim in patients with ITP in the extension study, peak serum concentrations were achieved at 7 to 50 hours (median, 14 hours). Serum concentrations varied among patients and were not correlated with dose. The $t_{1/2}$ ranged from 1 to 34 days (median, 3.5 days).[33]

In the first Phase I study of romiplostim, the *biologically active dose,* defined as that at which a ≥2-fold platelet increase was obtained in ≥2 subjects in a dose cohort, was found to be 2 μg/kg.[34] The authors stated that based on the findings from a review of previously published studies of 2 types of recombinant thrombopoietin (PEG-rHuMGDF and one expressed in Chinese hamster ovary cells), a dose associated with a 2-fold platelet increase in healthy volunteers was deemed to be an appropriate starting dose for the treatment of thrombocytopenia.[38] Some clinical investigators have suggested that initial clinical trials should employ doses that bracket this (2-μg/kg) dose.[34] In additional Phase I/II trials, romiplostim 1 and 2 μg/kg was associated with 1.5- to 2-fold increases in platelet counts.[35,36]

No formal drug interaction studies of romiplostim have been published,[33] and no drug interactions were found in the literature search.

Efficacy and Tolerability

Clinical Trials

Two Phase I/II open-label, dose-finding studies assessed the efficacy and tolerability of romiplostim in adults with chronic ITP.[36,37] The first study, by Newland et al,[36] enrolled patients with 2 of 3 pretreatment platelet counts of $<30 \times 10^9$ cells/L (in those who were not receiving background treatment with corticosteroids) or $<50 \times 10^9$ cells/L (in those who were receiving corticosteroids). Patients were assigned to 1 of 4 dose cohorts to receive romiplostim 30, 100, 300, or 500 μg SC on day 1 and then on day 15 (or day 22 if the platelet count on day 15 was $>50 \times 10^9$ cells/L). *Platelet response* was defined as a >2-fold increase from baseline in platelet count and a platelet count between 50 and 450×10^9 cells/L. Sixteen patients were enrolled (10 women, 6 men; age range, 20–84 years, median age, 50 years); 15 white, 1 black; median duration of ITP, 8 years; 4 patients per dose group). Three patients (19%) were receiving prednisone concurrently and 13 (81%) were splenectomized.

When a platelet count of 1062 × 10^9 cells/L was achieved in the patient who received the 500-μg dose, treatment with that dose was discontinued, the patient was withdrawn from the study, and the remaining 3 patients in that dose group were added to the 300-μg group, bringing the number of patients in this cohort to 7. Response data are presented in **Table II**. A platelet response was observed in 9 of 15 patients (60%) (1/4 [25%], 4/4 [100%], and 4/7 [57%] in the 30-, 100-, and 300-μg groups, respectively). An increase from baseline of ≥20 × 10^9 cells/L was found in 12 of 15 patients (80%), while an increase from baseline of ≥100 × 10^9 cells/L was achieved in 8 of 15 patients (53%). Peak platelet counts were achieved within 5 to 13 days (median, 10 days). On analysis with weight-based dose conversion, platelet response was achieved in 8 of 11 patients (73%) who received a dose ≥1 μg/kg. Treatment-related adverse events (AEs) were reported in 8 of 16 patients (50%), 2 of which were considered serious. These effects were worsening of thrombocytopenia after treatment and headache in 1 patient who received the 300-μg dose and a transient increase in serum lactic dehydrogenase in a patient who received the 500-μg dose. Additional AEs are presented in **Table II**.

The second study was a combined Phase I/II study.[37] Eligible patients were aged 18 to 65 years who had a history of ITP (duration, ≥3 months), had received ≥1 ITP treatments, and had a mean platelet count (based on 2 measurements) of <30 × 10^9 cells/L (patients who were not receiving background treatment with corticosteroids) or <50 × 10^9 cells/L (patients who were receiving background corticosteroids). Four patients per cohort were randomly assigned to receive romiplostim 0.2, 0.5, 1, 3, 6, or 10 μg/kg SC on days 1 and 15, or on days 1 and 22 if the platelet count on day 15 was >50 × 10^9 cells/L. In the Phase II double-blind study, patients were randomly assigned to receive treatment with romiplostim 1, 3, or 6 μg/kg SC or inactive vehicle (placebo) once weekly for 6 weeks. As in the trial by Newland et al,[36] *platelet response* was defined as a >2-fold increase from baseline in platelet count and between 50 and 450 × 10^9 cells/L.

Phase I enrolled 24 patients (17 women, 7 men; median age, 45 years [range, 21–65 years]; 22 white, 2 black; 4 patients per group). The median duration of ITP in Phase I was 6.2 years. Seven patients (29%) were receiving background treatment with corticosteroids, and 19 (79%) were splenectomized. None of the patients achieved a platelet response at doses <3 μg/kg, with the exception of 1 patient who had received rituximab 4 weeks before the study, a violation of the enrollment criterion that required 16 weeks to have expired since the last rituximab administration. Four of 12 patients (33%) who received a dose of 3 to 10 μg/kg achieved platelet response and platelet counts within the target range of 50 to 450 × 10^9 cells/L. In 3 others (25%), platelet count exceeded the upper limit of the target range, for a total of 7 of 12 patients (58.3%) in whom a platelet count of ≥50 × 10^9 cells/L was achieved. Platelet responses were found to be dose related. Mean peak platelet counts after the administration of the first dose were 163, 309, and 746 × 10^9 cells/L at 3, 6, and 10 μg/kg, respectively.

In Phase II, 21 patients were enrolled (15 women, 6 men; median age, 49 years [range, 19–64 years]; 14 white, 1 black, 6 other). The median duration of ITP was 5.2 years, 7 patients (33%) were receiving concurrent treatment with corticosteroids, and 14 (67%) were splenectomized. Romiplostim was administered in 17 patients (8 per dose group); and 4 patients received placebo. The 6-μg/kg cohort was closed after 1 patient's platelet count increased to 520 × 10^9 cells/L. This concern was confirmed when the study was unblinded. Seven of 8 patients (87.5%) who received the 1-μg/kg dose achieved a platelet response. There were 5 platelet responses in 8 patients (62.5%) who received the 3-μg/kg dose, 2 of which exceeded the upper limit of the targeted range of 50 to 450 × 10^9 cells/L and ≥2-fold the baseline count. Overall, in 12 of 16 patients (75%) who received 1 or 3 μg/kg of romiplostim, the target platelet range was achieved or exceeded. Mean peak platelet counts were 135 and 241 × 10^9 cells/L after the administration of doses of 1 and 3 μg/kg, respectively.

In the Phase I study, the most common AEs were contusions, ecchymosis, or both, which occurred in 67% of the 24 patients (6/12 [50%] at 0.2–1 μg/kg, and 10/12 [83%] at 3–10 μg/kg), and headache reported in 46% (6/12 [50%] at 0.2–1 μg/kg, and 5/12 [42%] at 3–10 μg/kg). Serious AEs were reported in 3 patients: 2 with the 0.2-μg/kg dose, and 1 with the 10-μg/kg dose. The 2 events that occurred at the 0.2-μg/kg dose resulted in hospitalization and were vertigo in one patient, and what the authors described as "life-threatening subdural hemorrhage" 21 days after the administration of the second dose in the

other patient. Neither of these effects was considered by the investigators to be drug related. Reductions in platelet counts to below baseline levels after treatment discontinuation were considered to be probably drug related.

Pivotal Trials

Two Phase III, multicenter, randomized, placebo-controlled, parallel-group trials were conducted in 125 patients with a history of chronic ITP and an insufficient response to corticosteroids, IVIg, and/or splenectomy.[39] Eligible patients were aged >18 years, had a mean initial platelet count $<30 \times 10^9$ cells/L, and had received corticosteroids (94%) or IVIg (80%) or were splenectomized (50%) (median time since splenectomy, 6.6 years). The patient population was 65% female, 82% white. One of these 2 studies involved 63 patients who were splenectomized ≥4 weeks before study entry, and the other enrolled 62 patients who were nonsplenectomized. They were randomized in a 2:1 ratio to receive subcutaneous romiplostim or placebo weekly for 24 weeks. The initial dose of romiplostim was 1 μg/kg/wk. Doses were adjusted to maintain platelet counts between 50 and 200×10^9 cells/L. The primary end point was a *durable platelet response,* defined as a platelet count $\geq 50 \times 10^9$ cells/L during ≥6 of the last 8 weeks of treatment. The maximum dose allowed was 15 μg/kg. Increases in current ITP treatment and/or the administration of rescue medication was allowed at any time. However, platelet responses that occurred within 8 weeks of the administration of rescue medication were not included in the analysis of efficacy or in the assessment of any other measures of platelet outcome. Patients who used rescue medications were not considered to have had a sustained durable platelet response.

Of the patients who were splenectomized, 95% (40/42) were randomly assigned to receive romiplostim and completed the study; 90% (19/21) received placebo and completed the study. One patient assigned to receive romiplostim withdrew consent, and the other was withdrawn due to an unspecified AE. The 2 patients assigned to receive placebo died during the study—1 from cerebral hemorrhage and 1 from pulmonary embolism. Of patients who were nonsplenectomized, 95% (39/41) were assigned to receive romiplostim and completed the study; 81% (17/21) received placebo and completed the study. Both patients assigned to receive romiplostim withdrew due to an unspecified AE; 2 patients assigned to receive placebo withdrew consent, 1 became pregnant, and 1 withdrew due to an unspecified AE. However, the authors included all patients assigned to receive romiplostim (n = 83) and all patients assigned to placebo (n = 42) in their response analysis. A platelet response was achieved in 25% of all romiplostim patients regardless of splenectomy status after 1 week and 50% after 2 to 3 weeks. During the last 8 weeks of the study (when durable response was assessed) in the romiplostim group, the median weekly platelet counts ranged from 56 to 85×10^9 cells/L in patients who were splenectomized and 63 to 96×10^9 cells/L in those who were not. The proportion of patients in whom a durable response was achieved was significantly greater with romiplostim than with placebo (49% vs 2%; $P < 0.001$).[40] Among patients who were splenectomized, 16/42 (38%) who received romiplostim achieved a durable platelet response compared with none of the patients who received placebo ($P = 0.001$); similar results were found in the nonsplenectomized subgroup (25/41 [61%] vs 1/21 [5%]; $P < 0.001$).

A secondary outcome was the assessment of a *transient platelet response,* defined as ≥4 weekly platelet responses without a durable platelet response over weeks 2 to 25. In the romiplostim group, a transient platelet response was achieved in 17 of 42 patients (40%) who were splenectomized and 11 of 41 patients (27%) of those who were not. Among splenectomized patients, the *overall platelet response,* defined as the combined end points of durable response plus transient response, was 79% in patients who received romiplostim compared with none of the patients who received placebo ($P < 0.001$). In nonsplenectomized patients, overall platelet responses of 88% and 14% were achieved in those who received romiplostim and placebo, respectively ($P < 0.001$). In all patients, regardless of splenectomy status, the overall platelet responses were 83% and 7% in the romiplostim and placebo groups ($P < 0.001$).

In splenectomized patients, platelet response was maintained for a mean duration of 12.3 weeks in the romiplostim group compared with 0.2 week in the placebo group ($P < 0.001$); in those who were nonsplenectomized, these values were 15.2 and 1.3 weeks, respectively ($P < 0.001$). In a combined analysis of the data from the splenectomized and nonsplenectomized subgroups, the mean durations of platelet response

were 13.8 and 0.8 weeks with romiplostim and placebo, respectively ($P < 0.001$).

Rescue medication (ie, an increased dose of concurrent ITP therapy or use of any new drug to increase platelet count) was administered in 22% and 60% of patients in the romiplostim and placebo groups, respectively ($P < 0.001$). In the splenectomized subgroup, corresponding values were 26% and 57% ($P = 0.018$); corresponding values were 17% and 62% in the nonsplenectomized group ($P < 0.001$). In the patients who were receiving ITP therapy at the start of the trial, 20 of 23 of those who received romiplostim (87%) and 6 of 16 of those who received placebo (38%) had had their doses reduced or treatment discontinued during the study. In a multivariate analysis, baseline weight <70 kg ($P = 0.011$) and no history of splenectomy ($P = 0.031$) were significantly associated with increased rates of durable response.

The duration of response was short in patients in whom treatment with romiplostim was discontinued. Platelet counts decreased to $<50 \times 10^9$ cells/L within 2 weeks of discontinuation of treatment with romiplostim in 73% of patients, and 7 of 83 patients (8.4%) who received romiplostim maintained a platelet count $>50 \times 10^9$ cells/L for >12 weeks after treatment was discontinued.

Extension Study

An open-label, single-arm extension study to assess the efficacy and tolerability of long-term romiplostim administration was begun in June 2004, with a scheduled completion date of December 2009.[41] An interim report was published in March 2009.[41] Eligible patients had completed a prior trial of romiplostim in ITP and had received romiplostim or placebo and had a platelet count $\leq 50 \times 10^9$ cells/L. Patients were excluded if they had an active malignancy diagnosed after enrollment in the prior romiplostim study, had a bone marrow stem cell disorder, or if <4 weeks had elapsed since any participation in a trial of any other investigational agent or since they last received an alkylating agent.

In the interim report, published after a median treatment duration of 69 weeks (maximum, 156 weeks),[41] 142 patients were enrolled and continued to receive romiplostim weekly or were switched to romiplostim after receiving placebo in a prior study. The median age was 53 years, 67% of the population was female, 83% were white, and 8% were Latino. Sixty percent were splenectomized, and 32% were receiving concurrent treatment of ITP at the start of the study. Patients were allowed to continue concurrent treatment with ITP medication that had been administered at a constant dose and schedule before the start of their initial study.

Romiplostim was administered subcutaneously at an initial dose of 1 μg/kg/wk in patients who were romiplostim naive or whose last dose was administered >24 weeks earlier. Those whose last dose was administered more recently continued to receive their most recent dose. Romiplostim doses were adjusted according to platelet counts. The target platelet range was 50 to 250×10^9 cells/L. Platelet response was defined as a platelet count $\geq 50 \times 10^9$ cells/L and double the baseline count in the absence of the use of rescue medication within the previous 8 weeks of this study. *Treatment failure* was defined as a platelet count $<20 \times 10^9$ cells/L for 4 consecutive weeks at a romiplostim dose of ≥10 μg/kg. Patients with treatment failure were withdrawn from the study unless the investigator believed that the patient was benefiting, and the sponsor provided permission for the patient to continue treatment.

A total of 142 patients initially received romiplostim. Eighteen patients (13%) did not achieve a platelet response, 8 of whom discontinued treatment, and 10 of whom continued to receive the drug. A platelet response was achieved in 30% after the administration of the first dose and in 51% by the third dose. The overall response rates were 47% to 74% up to week 144. At least 1 platelet response was achieved in 87% of the patients and responders; the proportion of time in which there was a platelet response was 67%. Median platelet counts increased rapidly during the first 4 weeks, then decreased more gradually through week 16. Median platelet counts ranged from 61 to 149×10^9 cells/L through week 144. The proportions of patients who achieved a platelet response in the subgroup of splenectomized patients compared with nonsplenectomized patients were 29% versus 32%, 49% versus 55%, 58% versus 65%, and 61% versus 81% at weeks 2, 4, 16, and 52, respectively. The median platelet counts in splenectomized and nonsplenectomized patients at weeks 12 to 84 were 58 to 106×10^9 cells/L and 96 to 209×10^9 cells/L, respectively. The between-subgroup difference in the duration of platelet response was nonsignificant. The findings from the interim report of the extension

study suggest that platelet response associated with romiplostim use might be sustained over the long term (up to 156 weeks) with weekly treatment, without the development of tolerance.

The authors reported that 32 patients received concurrent medication for ITP at the start of the study. At the cutoff time of their report, 16/32 (50%) had discontinued the medication and 11/32 (34%) had reduced the dose of concurrent ITP medication by ≥25%.

Specific Populations

Pregnancy

Romiplostim is classified in pregnancy category C (studies in animals have revealed AEs on the fetus [teratogenic, embryocidal, or other]), and there are no controlled studies in women, or studies in women and animals are unavailable. Drug treatment should be given only if the potential benefit justifies the potential risk to the fetus)[42] and has not been studied in pregnant women.[33] Animal studies found that the drug crossed the placenta and adverse fetal effects such as postimplantation loss, an increase in pup mortality, and thrombocytosis.[33] The manufacturer states that romiplostim should be used in pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.[33] The manufacturer has established a pregnancy registry to collect information about the effects of the drug during pregnancy.[33]

Pediatric and Elderly Populations

All of the patients in the clinical studies reviewed were ≥18 years of age. There are no published data on the use of romiplostim in children. Romiplostim was administered to 271 patients in clinical studies, 55 (20%) of whom were ≥65 years of age and 27 (10%) were ≥75 years of age.[33] There were no reported significant differences in efficacy or tolerability between older and younger patients in the placebo-controlled studies. The manufacturer states that in elderly patients, doses should be adjusted with caution because the prevalences of reduced hepatic, renal, or cardiac function, more concurrent disease, and the risk for other drug therapy are greater in the elderly.[33]

Renal/Hepatic Dysfunction

Romiplostim has not been studied in patients with renal or hepatic dysfunction. There are no available guidelines on dose adjustments in patients with renal or hepatic dysfunction.[33]

Tolerability

Across published clinical trials, romiplostim was generally well tolerated.[34–36,39] Most AEs were reported as mild to moderate.[36,37,39,41] No AEs were reported among the 12 patients who received single doses of romiplostim by the intravenous route in the first Phase I trial.[34] The most common AE reported with subcutaneous administration of a single dose in the Phase I/II studies were headache (13%–50%), arthralgias (31%), lower abdominal pain (17%), nasopharyngitis (13%–19%), diarrhea (13%), elevated liver enzyme concentrations (13%), and sore throat (13%).[34–36] Signs of bleeding were reported in the open-label Phase I/II study and included epistaxis (25%), petechiae (25%), ecchymosis (19%), injection-site hemorrhage (19%), and mouth hemorrhage (13%).[36]

The most common AEs reported in the pivotal trials are presented in **Table III**. All 84 patients who received romiplostim experienced ≥1 AE compared with 39 of 41 (95%) of those who received placebo. Bleeding events described as significant (severe, life-threatening, or fatal) occurred in 6 of 84 patients (7%) who received romiplostim and 5 of 41 patients (12%) who received placebo, all in patients with platelet counts $<20 \times 10^9$ cells/L. Two patients who received placebo died: 1 from cerebral hemorrhage and 1 from a pulmonary embolism. One patient who received romiplostim died from intracranial hemorrhage after beginning treatment with acetylsalicylic acid for thrombosis and after discontinuing treatment with romiplostim 1 day after study completion. Two serious AEs were considered by the investigators to be treatment related. Increased bone marrow reticulin developed in 1 patient who received romiplostim, and in the other patient (who had a history of extensive peripheral vascular disease, atrial fibrillation, and radial artery thromboembolectomy 8 months before the study, and who also received romiplostim) a right popliteal artery thrombosis developed and was treated with embolectomy and anticoagulation. That patient continued in the study.

Treatment-related AEs were reported in 34 patients (40.5%) and 11 patients (26.8%) who received romiplostim and placebo, respectively. Serious AEs were reported in 14 patients who received romiplostim (16.7%) and in 8 patients (19.5%) who received placebo.[40] AEs classified as serious and treatment related were reported in 2 patients (2%) who received romiplostim and in none of those who received placebo.[40]

Table III. Adverse events in the pivotal romiplostim trials.[39] Values are no. (%) of patients.

Event*	Romiplostim (n = 84)	Placebo (n = 41)
Headache	29 (35)	13 (32)
Fatigue	28 (33)	12 (29)
Epistaxis	27 (32)	10 (24)
Arthralgia	22 (26)	8 (20)
Contusion	21 (25)	10 (24)
Petechiae	14 (17)	9 (22)
Diarrhea	14 (17)	6 (15)
Upper respiratory infection	14 (17)	5 (12)
Dizziness	14 (17)	0
Insomnia	13 (15)	3 (7)
Myalgia	12 (14)	1 (2)
Back pain	11 (13)	4 (10)
Nausea	11 (13)	4 (10)
Extremity pain	11 (13)	2 (5)
Cough	10 (12)	7 (17)
Anxiety	9 (11)	5 (12)
Gingival bleed	9 (11)	5 (12)
Abdominal pain	9 (11)	0
Nasopharyngitis	7 (8)	7 (17)
Ecchymosis	6 (7)	6 (15)
Serious events		
Significant bleeding event†	6 (7)	5 (12)
Death	1 (1)‡	3 (7)§
Other serious treatment-related event	2 (2)‖	0

* Almost all adverse events were considered mild or moderate.

† Defined as severe, life-threatening, or fatal, and all occurred in patients with platelet counts <20 × 10^9 cells/L.

‡ One death from intracranial hemorrhage 1 day after study completion (after initiation of treatment with acetylsalicylic acid for thrombosis and discontinuation of treatment with romiplostim).

§ Determined by the authors to be non–treatment related. Causes: cerebral hemorrhage, pulmonary embolism, and atypical pneumonia after a trauma-associated intracranial hemorrhage 5 weeks after study completion.

‖ Determined by the authors to be treatment related: increased bone marrow reticulin and popliteal artery thrombosis (1 patient each).

Compared with placebo, romiplostim was associated with higher prevalences of headache (35% vs 32%), fatigue (33% vs 29%), epistaxis (32% vs 24%), arthralgia (26% vs 20%), dizziness (17% vs 0%), insomnia (15% vs 7%), myalgia (14% vs 2%), extremity pain (13% vs 5%), and abdominal pain (11% vs 0%).

Three patients experienced thromboembolic events (2 with romiplostim [popliteal artery thrombosis (1) and cerebrovascular accident (1)], 1 with placebo [fatal pulmonary embolism]).[39] Both of these patients who received romiplostim were elderly and had a history of vascular disease. The patient who experienced a cerebrovascular accident (CVA) had a history of cerebrovascular disease. At the time of the AEs, the platelet count in the patient in whom popliteal artery thrombosis developed was 11 × 10^9 cells/L, and the

patient in whom the CVA developed had a platelet count of 107 × 10^9 cells/L. The authors determined that the CVA was not related to the use of romiplostim, but they did not conclude that the popliteal artery thrombosis was drug related or due to the platelet count.

Thrombocyte counts lower than baseline were reported on discontinuation of romiplostim in 1 patient in the Phase I/II study and in 10 patients in the extension trial.[36,41] Leukemia developed in 4 of 44 patients (9%) with myelodysplasia who received romiplostim in another Phase I/II study.[43,44] Based on those findings, the authors recommended that romiplostim treatment be avoided in patients with myelodysplasia due to an increased risk for acute myelogenous leukemia.[43]

AEs were common in the interim report of the extension study, with 95% of patients (135/142) reporting ≥1 AE.[41] The most common were headache (37%), nasopharyngitis (32%), contusion (30%), epistaxis (30%), fatigue (30%), arthralgia (25%), and diarrhea (25%). In most patients, the AEs were classified as mild or moderate. Serious AEs were reported in 31% of patients (44/142) and included thrombocytopenia (10/142 patients [7%]), increased bone marrow reticulin (5/142 patients [4%]), and congestive heart failure (3/142 patients [2%]), 2 cases each of severe headache and migraine headache, and 1 patient each with abdominal pain, platelet count >1000 × 10^9 cells/L, platelet count of 1183 × 10^9 cells/L, blindness, papilledema, diarrhea, injection-site irritation, muscle spasms, and bone pain, all of which resolved. In addition, 1 patient each experienced anemia (continued), monoclonal gammopathy of unknown significance (continued), and fatigue (status not known). Three additional patients experienced increased bone marrow reticulin, 1 case of which was not considered to be serious and 2 of which were described as having been noted in the patients' records but not described as an AE, bringing the number of cases of increased marrow reticulin to 8 of 142 (5.6%). A total of 19 serious AEs occurring in 13 patients (9.2%) were considered treatment related.

Additional serious AEs reported in the extension study included bleeding and thrombotic/thromboembolic events. There were 14 serious bleeding events in 12 patients (8.5%). One (vaginal bleeding) was considered treatment related. Platelet counts were ≤30 × 10^9 cells/L at or near the time of each bleeding event, with 1 exception. The proportion of patients who experienced bleeding events decreased during the course of the study, from 42% during the first 24 weeks, to 29%, 23%, and 20% during weeks 25 to 48, 48 to 72, and 72 to 96, respectively.[41]

Twelve thrombotic/thromboembolic events were reported in 7 patients (4.9%), 5 cases of which were thought to be treatment related. These events included 1 case each of deep venous thrombosis, septic thrombophlebitis, transient ischemic attack, myocardial infarction, and coronary artery occlusion. Six of these 7 patients had a history of ≥1 risk factor for thrombosis before the first administration of romiplostim.[41]

Because romiplostim is a protein, there was a theoretical concern that patients might develop antibodies that could cross-react with endogenous TPO. All of the clinical trials reviewed monitored subjects for the development of neutralizing or binding antibodies to romiplostim or endogenous TPO.[34–37,39,41] No neutralizing antibodies to romiplostim or TPO were found in the Phase I/II studies or in the pivotal trials.[34–37,39] One patient in the extension study transiently developed neutralizing antibodies to romiplostim but not to TPO. Antibody tests were negative at a follow-up 4 months later. An immunogenicity assessment of data from 10 clinical trials analyzed the blood of 236 subjects who received romiplostim for antibodies that could neutralize the effects of romiplostim or TPO.[45] At baseline, 17 patients (7%) tested positive for romiplostim antibodies, and 12 (5%) tested positive for antibodies to TPO. After treatment, 25 (10.5%) had binding antibodies to romiplostim and 12 (5%) had binding antibodies to TPO. Neutralizing antibodies to romiplostim developed in 1 patient (0.4%), and neutralizing antibodies to TPO were not reported in any of the patients. No clinical complications associated with the presence of antibodies were reported.

A concern with romiplostim is the risk for increased reticulin or collagen formation in the bone marrow. Most patients who receive romiplostim have not undergone a marrow evaluation, so the true incidence of this effect is unknown.[34–36,39,41] An increase in marrow reticulin was reported in 1 patient in the pivotal trials. That patient had an elevated baseline bone marrow reticulin concentration, which worsened after 7 weeks of romiplostim and was near-normal at a repeat biopsy analysis 14 weeks after treatment when the drug was discontinued. In the extension study, bone marrow was examined in 16 patients, 9 of whom participated in a prospective study to assess the effects of romiplostim on marrow morphology.[41,46]

Bone marrow was assessed at the investigator's discretion in the patients who were not part of the prospective study, and was recommended at the investigator's discretion if abnormalities were detected in a peripheral blood smear or if there was a loss of response to romiplostim treatment despite increasing doses. The following scale was used for reticulin grading: 0 = none; 1 = fine fibers; 2 = diffuse fine fiber network; 3 = diffuse fiber network with scattered coarse fibers; and 4 = areas of collagen. There were 8 bone marrow biopsies obtained at baseline (7 with no reticulin staining and 1 with mild reticulin staining). Baseline and follow-up marrow biopsy results were available in 6 patients; all were graded as 0 or 1 at baseline, and 5 of the 6 were negative for reticulin staining on follow-up. In 1 patient, the staining grade changed from 0 or 1 at baseline to 1 or 2 after 3 months of treatment. Increased marrow reticulin was reported in 7 patients who were not part of the prospective marrow study. No symptoms were reported in any of the patients with increased marrow reticulin, but the marrow findings led to treatment discontinuation in 2 patients. Increased marrow reticulin was associated with multiple prior ITP treatments, history of splenectomy, administration of relatively high doses of romiplostim (5–18 μg/kg), minimal platelet response to romiplostim, and possibly the presence of nucleated red cells. A pathologic review by Beckman and Brown[47] of the bone marrow biopsy specimens from 100 patients with normal hematology reported that 31 of 100 patients (31%) had reticulin grade 1 or 2. Reticulin grade 1 or 2 were reported in 66% of patients in a retrospective examination of bone marrow biopsies in 40 patients with ITP.[48]

Data from 8 clinical trials, including Phase III studies and the interim report of the extension study, were analyzed in a pooled analysis of the long-term tolerability of romiplostim.[49] A total of 229 patients were analyzed (219 who received romiplostim and 46 who received placebo, with 36 who started to receive placebo and were later switched to romiplostim counted in both groups). An increase in marrow reticulin was reported in 10 of 219 patients (4.5%) who received romiplostim.

Tolerability concerns cited by the FDA on the announcement of approval of romiplostim included the risk for fibrous deposits in the bone marrow, depressed platelet counts on treatment discontinuation, thrombotic events due to elevated platelet counts, and acute leukemia in patients with myelodysplastic syndrome.[44] The FDA required that the manufacturer develop a risk-evaluation and mitigation study to assess and address the risks associated with long-term romiplostim treatment.[44] The program requires all prescribers, patients, hospitals, and health care systems to enroll.[50] Patients are required to be given a medication guide before treatment initiation and before the administration of each dose and to receive counseling on the risks and benefits of romiplostim treatment. Providers must register each patient with the program and agree to provide long-term follow-up and AE data every 6 months. Patients should be seen every 6 months for assessments of treatment response and tolerability and to determine whether treatment should be continued for an additional 6 months. Health care facilities must maintain drug records that document receipt and dispensing of the drug, as well as any drug accountability and reconciliation records.

Dosage and Administration

The commercial product is supplied as a sterile, preservative-free, lyophilized white powder for subcutaneous injection. It is available in 2 vial sizes containing 250 or 500 μg of romiplostim per vial. The vials should be refrigerated and protected from light and are intended for single use. The manufacturer recommends that any unused portion be discarded.[33]

Romiplostim is dosed based on actual body weight, with a recommended initial dose of 1 μg/kg. Subsequent doses are based on platelet counts. Weekly increases of 1 μg/kg are recommended until a platelet count of $\geq 50 \times 10^9$ cells/L is achieved. In clinical studies, most responders achieved and maintained platelet counts $\geq 50 \times 10^9$ cells/L at a median dose of 2 μg/kg.[33] The recommended maximum weekly dose is 10 μg/kg. The dosing adjustments recommended by the manufacturer are presented in **Table IV**. Although romiplostim is FDA approved for administration by a health care professional, a long-term extension study reported that romiplostim administered by self-injection was effective in patients with chronic ITP.[51]

Costs

The average wholesale prices of romiplostim are $1062.50 for a single-use 250-μg vial and $2125.00 for a vial containing 500 μg.[52] In a 75-kg patient who receives a 2-μg/kg weekly dose, the acquisition cost

Table IV. Romiplostim administration guidelines.[33]

Administration Parameter	Dose*
Initial dose	1 μg/kg/wk SC
Maintenance dose by platelet count	
$<50 \times 10^9$ cells/L	Increase dose by 1 μg/kg/wk†
$50–200 \times 10^9$ cells/L	Maintain current dose
$>200 \times 10^9$ cells/L for 2 consecutive weeks	Reduce dose by 1 μg/kg weekly
$>400 \times 10^9$ cells/L	Hold and continue to monitor the platelet count weekly; after the platelet count decreases to $<200 \times 10^9$ cells/L, resume treatment at a dose that is reduced by 1 μg/kg/wk

*Maximum recommended individual dose, 10 μg/kg.
† Titrate dose to achieve platelet count $\geq 50 \times 10^9$ cells/L.

would be $4250.00 per month. This cost does not include drug administration costs (eg, needles, syringes, nursing time), which would increase the overall cost of treatment. A reimbursement assistance program is available through the manufacturer.[53]

Quality of Life

The impact of romiplostim on health-related quality of life (QOL) in patients with chronic ITP was assessed in the 2 pivotal studies described earlier.[54] The investigators employed a self-administered ITP Patient Assessment Questionnaire (ITP-PAQ), developed specifically for adults with chronic ITP. The ITP-PAQ contained 44 questions organized into 10 scales—physical health (activity, bother, fatigue, and symptoms), emotional health (fear and psychological health), social activity, work, women's reproductive health, and overall QOL. The ITP-PAQ was administered before (baseline) and after 4, 12, and 24 weeks of treatment. A total of 125 patients participated in the study, 84 of whom received romiplostim and 41 of whom received placebo. Sixty-three had undergone splenectomy and 62 had not.

Baseline ITP-PAQ scores were comparable between the romiplostim and placebo groups, suggesting a similar QOL before the initiation of treatment. Baseline scores on 7 of 10 scales (bother, fear, psychological health, social activity, symptoms, work, and overall QOL) were significantly lower in the subgroup of splenectomized patients compared with nonsplenectomized patients ($P < 0.05$). After 24 weeks, scores on 4 of the 10 scales were significantly improved in the splenectomized patients who received romiplostim compared with those who received placebo (bother, $P = 0.013$; social activity, $P = 0.015$; symptoms, $P = 0.034$; and women's reproductive health, $P = 0.018$). In the nonsplenectomized subgroup, only the activity scale score was significantly improved with romiplostim compared with placebo ($P = 0.046$). In a pooled analysis of the data from the combined splenectomized and nonsplenectomized subgroups, scores on 7 of the 10 scales were significantly improved in patients who received romiplostim compared with placebo ($P < 0.05$). The investigators compared test scores in patients who continued to receive ITP treatment for the entire study period with those from patients who had discontinued treatment. The differences in scores on bother, symptoms, and work, although not reported as statistically significant (P not reported), were consistent with poorer functioning in those who continued ITP treatment for 24 weeks. If continuation of prior ITP therapy resulted in lower QOL scores on some scales, it is also possible that higher QOL scores seen among romiplostim patients may have been due to the fact that these patients were able to discontinue use of other medications (eg, corticosteroids, azathioprine, danazol) and not due to an effect of romiplostim use.

The study was limited by the small number of patients in each arm and by its short duration. The findings from this study suggested that romiplostim might improve the QOL in patients with chronic ITP. More

study is needed to determine the role of romiplostim in the treatment of this disorder.

Monitoring Parameters/Discontinuation of Therapy

Patients considered for romiplostim therapy should have baseline complete blood counts (CBCs), platelet counts, and peripheral blood smears prior to institution of therapy.[33] The manufacturer recommends weekly assessment of CBCs, platelet counts, and peripheral blood smears during the initial dose adjustment period of treatment.[33] These studies should be conducted monthly once the stable romiplostim dose has been established.[33] Patients should be counseled to inform their health care providers if they develop any bruising or bleeding while receiving romiplostim. The manufacturer recommends discontinuation of treatment if the platelet count has not increased to a level to avoid clinically significant bleeding after 4 weeks of treatment at the maximum weekly dose of 10 μg/kg.[33] Because rebound thrombocytopenia has been reported after discontinuation of romiplostim, with resolution within 14 days, CBCs and platelet counts should be assessed for 2 weeks after romiplostim discontinuation.[33]

Because romiplostim has been associated with an increased risk for or progression of reticulin fiber in the bone marrow, the blood smear should be examined before treatment initiation to determine the baseline level of cellular morphologic abnormalities.[55] Once a stable romiplostim dose has been achieved, blood smears should be examined monthly for new/worsening morphologic abnormalities.[55] If a morphologic abnormality develops or worsens, romiplostim treatment should be discontinued and a bone marrow biopsy should be considered.[55]

At the time of patient enrollment, health care providers are also required to submit baseline patient data.[55] A specialist then contacts the health care provider twice a year to verify patient enrollment and to collect tolerability data. The health care provider is asked to complete a questionnaire on each patient which asks whether the patient has experienced any AEs while receiving romiplostim. If a serious event is reported, the health care provider is contacted by a romiplostim representative for additional information.

When a patient discontinues treatment with romiplostim, a program discontinuation follow-up form[55] should be submitted to the manufacturer at the time of discontinuation and 6 months later.

DISCUSSION

Romiplostim is the first available drug in a recently developed class of agents, the thrombopoietics, which stimulate the TPO receptor to increase platelet production. Romiplostim administration has been associated with durable platelet responses in adult patients with chronic ITP with a history of insufficient response to treatment with corticosteroids, IVIg, or splenectomy. An interim report of the findings from the ongoing extension trial found that responses may be sustained over 156 weeks of continuous therapy. Although not a part of the outcome criteria in the extension study, the decline in bleeding events over time suggests that a platelet response may be correlated with clinical benefit.

Although romiplostim has been generally well tolerated in clinical trials, there are concerns about the risk for reticulin fibrosis and thrombosis. Because most thrombotic events in the extension trial occurred in patients with risk factors for thrombosis, it may be appropriate to use romiplostim with caution in such patients. Sustained beneficial effects have been associated only with continued administration of the drug. Decreases in platelets to pretreatment counts or, in some cases, a transient decrease to less than pretreatment counts, have been found within 2 weeks after treatment discontinuation. Romiplostim is FDA approved for the treatment of thrombocytopenia in patients with chronic ITP with a history of insufficient response to corticosteroids, immunoglobulins, or splenectomy. Its use in the treatment of myelodysplastic syndrome[43,56] and chemotherapy-associated thrombocytopenia[57,58] are being investigated. Additional roles for romiplostim may be to defer splenectomy with the hope of a spontaneous remission[59,60] and to prepare patients for elective surgery or splenectomy.[60]

Although the exact role of romiplostim in the management of ITP has not been determined, this agent has been associated with improvement in these patients with a history of insufficient response to corticosteroids, immunoglobulins, or splenectomy. It may also have a role in patients who would be candidates for splenectomy but for whom splenectomy is contraindicated due to comorbidities or advanced age.[60]

Limitations

Perhaps the greatest limitation to a review of a recently developed drug is the limited clinical data available at the time of FDA approval. The manufacturer reports that, at the time of FDA approval, only 271 patients had received romiplostim in ITP clinical studies.[33] As would be expected in such a small sample size, no data in children were available. Although there were some elderly patients in the clinical trials, there was no separate analysis of the efficacy or tolerability of the drug in the older patient population. There are also no data on the use of romiplostim in patients with renal and/or hepatic dysfunction. Therefore, no dose adjustments can be recommended in these patients. There are also no data on the use of the drug in pregnant or nursing women. The clinical trials cited here were primarily focused on the ability of romiplostim to assess platelet counts and on the AEs associated with its use.[36,37,39,40] None of the trials assessed the impact of romiplostim on survival in patients with chronic ITP. In most[34,36,37,39] of the trials, romiplostim was administered for a short period of time. The longest experience with romiplostim was reported in the extension trial where some of the patients were treated for up to 3 years. There are, therefore, limited data on the efficacy and tolerability of long-term use of this agent. There are also no guidelines as to how long-term treatment should be continued. These patients had undergone prior therapy for ITP and many received concurrent therapy while they received romiplostim. The activity of romiplostim as a first-line agent in patients with ITP is, therefore, unknown.

CONCLUSIONS

Romiplostim is the first drug in a recently developed class of agents with the potential to improve the management of refractory chronic ITP. Romiplostim was associated with increased platelet counts in these patients with a history of insufficient response to corticosteroids, IVIg, or splenectomy. A reduction in concurrent treatments for ITP might be possible in some patients who receive romiplostim. Romiplostim might reduce the risk for bleeding episodes in patients with ITP. The effect appears to be sustained only during administration of the drug, as platelet counts decrease—sometimes to below pretreatment counts—quickly after treatment with romiplostim is discontinued. Although most AEs associated with the use of romiplostim have been reported as mild to moderate, there are a few potentially serious effects, especially increased bone marrow reticulin and thrombosis, that need to be further assessed. In 1 trial, romiplostim was associated with increased myeloblasts in patients with myelodysplastic syndrome, with progression to acute myelogenous leukemia in 2 patients. The effects of romiplostim on hematologic malignancies needs additional evaluation. Long-term data are needed to determine the long-term tolerability and the true role of romiplostim in the management of chronic ITP.

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