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ORIGINAL REPORT

Safety and Efficacy of Romiplostim in Patients With Lower-Risk Myelodysplastic Syndrome and Thrombocytopenia

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ABSTRACT

Purpose
To assess the safety and efficacy of romiplostim, a peptibody that increases platelet production, for treatment of thrombocytopenic patients with myelodysplastic syndromes (MDS).

Patients and Methods
Eligible patients had lower-risk MDS (International Prognostic Scoring System low or intermediate 1), a mean baseline platelet count $\leq 50 \times 10^9$/L, and were only receiving supportive care. Patients received three injections of 300, 700, 1,000, or 1,500 μg romiplostim at weekly intervals. After evaluation of platelet response at week 4, patients could continue to receive romiplostim in a treatment extension phase for up to 1 year.

Results
All 44 patients who enrolled completed the treatment phase; 41 patients continued into the extension phase. Median platelet counts increased throughout the study, from fewer than 30×10^9/L at baseline to 60, 73, 38, and 58×10^9/L at week 4 for the 300-, 700-, 1,000-, and 1,500 -μg dose cohorts, respectively. A durable platelet response (per International Working Group 2000 criteria for 8 consecutive weeks independent of platelet transfusions) was achieved by 19 patients (46%). The incidence of bleeding events and platelet transfusions was less common among patients who achieved a durable platelet response than those who did not (4.3 *v* 39.3 per 100 patient-weeks). Forty-three patients (98%) reported one or more adverse events. Treatment-related serious adverse events were reported in five patients (11%), all of whom were in the 1,500-μg dose cohort. Two patients progressed to acute myeloid leukemia during the study. No neutralizing antibodies to either romiplostim or endogenous thrombopoietin were seen.

Conclusion
Romiplostim appeared well-tolerated in this study and may be a useful treatment for patients with MDS and thrombocytopenia.

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INTRODUCTION

Myelodysplastic syndromes (MDSs) are a heterogeneous group of clonal hematologic malignancies of pluripotent hematopoietic stem cells, characterized by peripheral blood cytopenias and ineffective hematopoiesis.[1,2] Progressive hematopoietic failure may lead to anemia, thrombocytopenia, and leukopenia. The prognosis of patients with MDS is poor; patients die either from complications associated with cytopenias (infections and bleeding) or from transformation to acute myeloid leukemia (AML), which occurs in 10% to 70% of patients, more commonly in higher-risk patients.[3] The median time to 25% AML progression differs by International Prognostic Scoring System (IPSS) risk group: low-risk patients, 9.4 years; intermediate-1–risk patients, 3.3 years; intermediate-2–risk patients, 1.1 years; and high-risk patients, 2 months.[4]

At the time of diagnosis, 30% of patients have thrombocytopenia, with $\leq$ 10% initially experiencing serious bleeding. The incidence of life-threatening thrombocytopenia (platelet count $< 20 \times 10^9$/L) at presentation has been documented in approximately 12% of patients with low or intermediate-1 risk MDS.[5] Platelet function may be abnormal in MDS patients,[6,7] making the presence of moderate to severe thrombocytopenia of greater concern.[5,6]

Thrombocytopenia is an independent adverse prognostic factor for survival in MDS,[8] and increased severity of thrombocytopenia correlates with shorter time to AML progression.[9] Platelet transfusions are the only current treatment option,

and a recent survey of physicians in the United States showed that 6% to 33% of patients with MDS were platelet transfusion dependent.[10] Platelet transfusions are associated with adverse effects that include febrile or allergic transfusion reactions, transmission of bacterial and viral infections, transfusion-related acute lung injury, and most commonly in patients with MDS, alloimmunization—ultimately rendering platelet transfusions ineffective.[11,12] Therefore, new therapeutic approaches to treat thrombocytopenia in patients with MDS would be advantageous.

Romiplostim is a peptibody that increases platelet production through the thrombopoietin (TPO) receptor (c-Mpl). Clinical studies showed that romiplostim increases platelet counts in healthy individuals and in patients with chronic immune thrombocytopenia.[13,14] This study evaluated the efficacy and safety of romiplostim in thrombocytopenic patients with low- or intermediate-1–risk MDS.

PATIENTS AND METHODS

Study Design and Patients

This was a phase I/II, multicenter, open-label, sequential-cohort, dose-escalation study (ClinicalTrials.gov identifier NCT00303472). Institutional review boards at each study-site approved the protocol; all subjects provided written informed consent.

Eligible patients were ≥ 18 years old and had the following: a diagnosis of MDS using WHO classification; IPSS low- or intermediate-1–risk MDS; mean baseline platelet count ≤ 50×10^9/L; Eastern Cooperative Oncology Group status of 0 to 2; and adequate renal and hepatic functions. Key exclusion criteria included: current treatment for MDS except transfusions and erythropoiesis-stimulating agents; clinically significant bleeding within 2 weeks of screening; prior malignancy (except controlled prostate cancer, in situ cervical cancer, or basal cell skin cancer) unless disease free ≥ 3 years before screening; previous treatment with recombinant TPO or TPO mimetic; receipt of antithymocyte globulin within 6 months of screening; receipt of hypomethylating agents, immunomodulating agents, histone deacetylase inhibitors, cyclosporine, or mycophenolate within 6 weeks of screening; receipt of interleukin-11 or any investigational drug or device within 4 weeks of screening; or current use of granulocyte growth factors.

Procedures and Assessments

Patients were enrolled into one of four sequential cohorts of 300, 700, 1,000, and 1,500 μg romiplostim, administered subcutaneously once weekly. During the 4-week treatment phase, patients received romiplostim for 3 weeks and completed follow-up assessments in week 4. Dose-escalation continued until at least two of five patients per cohort experienced a treatment-related dose-limiting toxicity (any treatment-related grade 3 or 4 toxicity). Patients who completed the treatment phase were eligible to receive romiplostim for up to 1 year in an extension phase. Dose-escalation was allowed in the extension phase in patients who did not achieve a complete platelet response in the treatment phase. All patients had an end-of-study visit 4 weeks after their last romiplostim administration.

CBCs and blood chemistry analyses were performed weekly and at the end-of-treatment. Bone marrow morphology and histology from samples taken pretreatment and at end-of-study visits were reviewed by a central laboratory. An AML diagnosis was made using WHO criteria of ≥ 20% blasts in either the bone marrow or peripheral blood that persisted for ≥ 4 weeks after drug discontinuation.[15] Evidence of chloroma also constituted progression to AML. Patients who did not fulfill WHO criteria but subsequently received treatment for AML were considered to have progressed to AML. Transient increases in blast counts ≥ 20% that resolved within 4 weeks were not considered AML transformation.

Efficacy was evaluated by the proportion of patients achieving a platelet response during the treatment period using International Working Group (IWG) criteria.[16] A complete platelet response was defined as an increase of platelet count to higher than 100×10^9/L; a major platelet response was defined as an increase of platelet count by higher than 30×10^9/L. Additional analyses to evaluate a durable platelet response were performed using IWG 2006–defined criteria,[17] in which a hematologic improvement in platelets (HI-P) was defined as either an increase ≥ 30×10^9/L for patients with a baseline platelet count of higher than 20×10^9/L, or an increase from lower than 20×10^9/L to ≥ 20×10^9/L and by at least 100%. A durable platelet response was defined as HI-P for ≥ 8 consecutive weeks; therefore, only patients who entered the extension phase were evaluated for this end point. Platelet counts obtained within 72 hours of platelet transfusions were not evaluated for durable platelet responses. A second efficacy end point was the proportion of patients who received platelet transfusions.

Safety was evaluated from the incidence and severity of adverse events, determined according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0, and included evaluation of antibody status. Progression of disease to AML was not considered an adverse event. Bleeding episodes were recorded as adverse events, and bleeding adverse events grade 2 or higher severity were considered clinically significant. The maximum tolerated dose (MTD) of romiplostim was defined as the highest dose at which ≤ 33% of patients in the treatment phase experienced treatment-related grade 3 to 4 toxicity and showed an acceptable safety profile in the extension phase.

Statistical Analysis

Patients who remained on study for ≥ 4 weeks in the treatment phase were included in the efficacy analysis. Patients who received ≥ 1 dose of romiplostim were included in the safety analysis until their end-of-study visit, 4 weeks after the last dose of romiplostim. The patient incidence of a particular adverse event was defined as the number of patients experiencing the adverse event divided by the total number of patients. The adverse event incidence per 100 patient-weeks was calculated from the total number of adverse events, divided by the total number of patient-weeks on study, multiplied by 100.

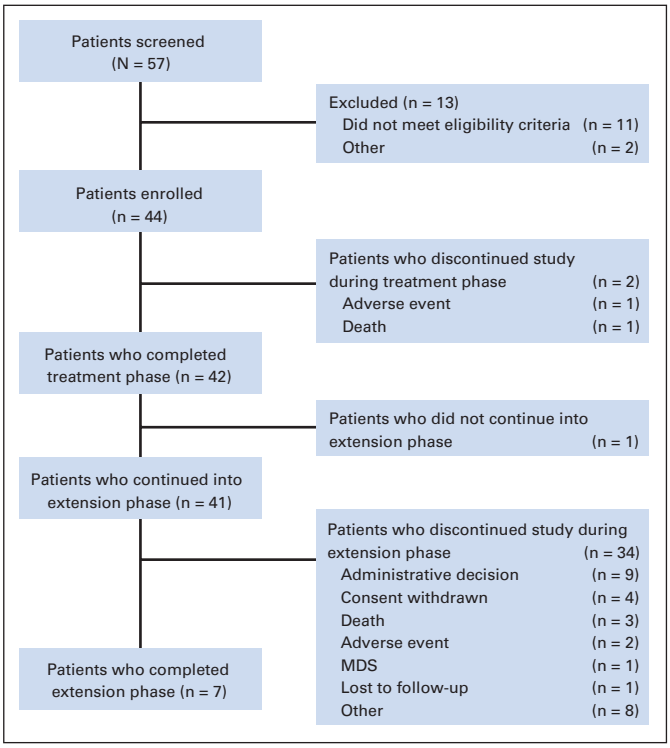

Fig 1. Patient disposition. All patients completed treatment in the treatment phase and were included in both the efficacy and safety analyses. Two patients discontinued the treatment phase either on or before their end-of-study visit. One patient completed the treatment phase and elected not to continue into the extension phase. MDS, myelodysplastic syndrome.

RESULTS

Study Population

All 44 enrolled patients completed 4-week treatment with romiplostim (Fig 1). Two patients discontinued the treatment phase after 4 weeks: one experienced an adverse event of transient blast count increase reported at their end-of-study visit, and one died after completing 4 weeks treatment but before the end-of-study visit (cause of death was MDS), another patient completed the treatment phase but elected not to enter the extension phase. Forty-one patients participated in the extension phase; 28 discontinued the study (Fig 1). The mean duration of treatment was 30 weeks (standard deviation ± 22 weeks).

Patient demographics are presented in Table 1. In the year before enrollment, 68% of patients had received platelet transfusions and 32% experienced a bleeding event. A higher percentage of patients in the 700 μg-cohort had an IPSS score ≥ 1.0 than the other cohorts.

Efficacy: Platelet Response

Median platelet counts increased throughout the study (Fig 2), from less than 30×10^9/L at baseline to 60, 73, 38, and 58×10^9/L at week 4 for the 300-, 700-, 1,000-, and 1,500-μg dose cohorts, respectively. Median platelet counts remained above baseline in all dose cohorts for the remainder of the study. During the treatment phase, 20 patients (45%) had either a complete or major platelet response by IWG 2000 criteria; four (25%) of 16 patients with a baseline platelet

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	Romiplostim (μg) 300 No.	300 %	700 No.	700 %	1,000 No.	1,000 %	1,500 No.	1,500 %	All Patients No.	All Patients %
No. of patients	6		11		11		16		44	
Sex										
Male	6	100	6	55	9	82	11	69	32	73
Female	0		5	45	2	18	5	31	12	27
Median age, years	76.0		70.0		74.0		72.0		74.5	
Minimum	75		49		48		31		31	
Maximum	84		81		89		86		89	
Race										
White	5	83	11	100	9	82	14	88	39	89
Other	1	17	0		2	18	2	12	5	12
ECOG status										
0	4	67	4	36	6	55	7	44	21	48
1	2	33	7	64	4	36	8	50	21	48
2	0		0		1	9	1	6	2	5
MDS diagnosis*										
RA	5	83	2	18	3	27	4	25	14	32
RARS	0		1	9	0		1	6	2	5
RAEB-1	0		2	18	0		3	19	5	11
RCMD	0		3	27	8	73	5	31	16	36
RCMD-RS	1	17	1	9	0		1	6	3	7
MDS-U	0		1	9	0		2	13	3	7
MDS with del (5q)	0		1	9	0		0		1	2
IPSS score†										
0	1	17	3	27	7	64	4	25	15	34
0.5	5	83	4	36	3	27	8	50	20	46
1.0	0		3	27	1	9	2	13	6	14
> 1.0	0		1	9	0		1	6	2‡	5
Prior therapies for MDS										
Any	1	17	5	46	7	64	7	44	20	46
Erythropoietic growth factor	3	50	1	9	1	9	7	44	12	27
Granulocyte growth factor	0		2	18	1	9	5	31	8	18
Median duration of MDS since diagnosis, years	—		—		—		—		1.3	
Range									0.02-27.74	
Patients with a bleeding event in the past year	2	33	4	36	3	27	5	31	14	32
Patients who received a platelet transfusion in the past year	4	67	7	64	9	82	10	63	30	68

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MDS, myelodysplastic syndrome; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess of blasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, RCMD with ringed sideroblasts; MDS-U, MDS unclassified; IPSS, International Prognostic Scoring System.

*WHO classification. Diagnosis was determined by the investigator.

†IPSS scoring for risk groups: 0 = low; 0.5 to 1.0 = intermediate 1; 1.5 to 2.0 = intermediate 2; ≥ 2.5 = high. IPSS determination was missing from one patient receiving romiplostim 1,500 μg.

‡Two patients with an IPSS score greater than 1 were initially recorded as having an IPSS score of 1 upon study entry, but were subsequently reclassified as IPSS 1.5. Data from all patients treated with romiplostim on study have been reported in the manuscript.

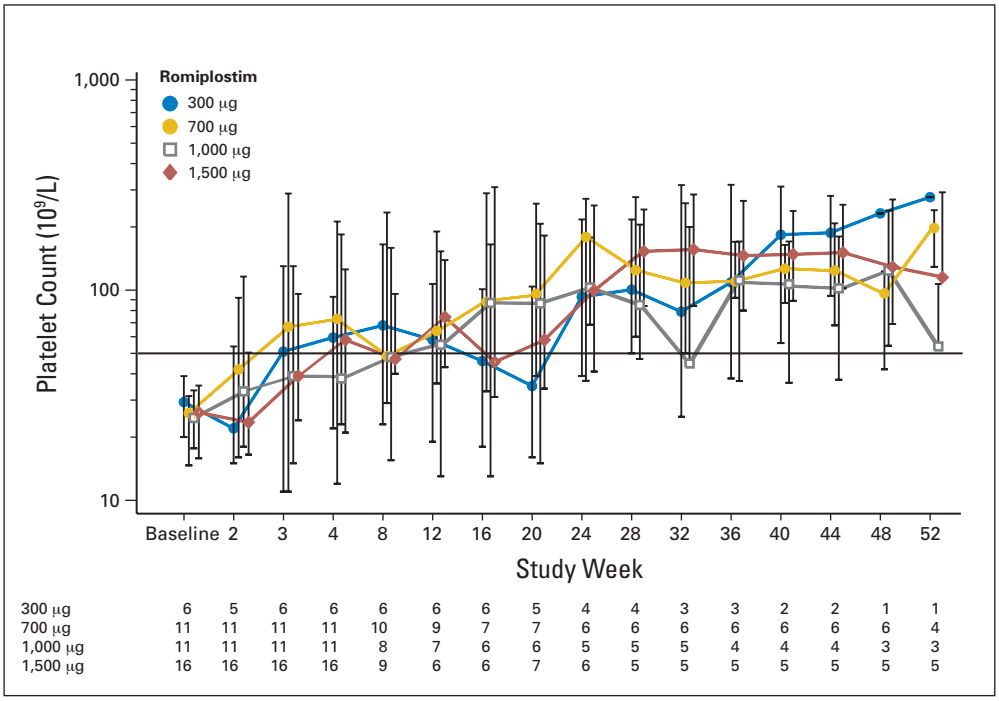

Fig 2. Median platelet counts over time. Median (25th [Q1] and 75th [Q3] percentiles) platelet counts by study week. Median platelet counts in all dose cohorts increased steadily over time on treatment through week 52.

count $\leq 20 \times 10^9$/L and 16 (57%) of 28 patients with a baseline platelet count higher than 20×10^9/L (Table 2). The proportion of patients experiencing either a complete or major platelet response was similar among dose cohorts.

Durable Platelet Response

Most patients (41 of 44; 93%) entered the extension phase and were evaluated for a durable platelet response. A durable platelet response was achieved in 19 patients (46%); six (43%) of 14 patients with a baseline platelet count $\leq 20 \times 10^9$/L, and 13 (48%) of 27 patients with a baseline platelet count $\geq 20 \times 10^9$/L. The time period to achieve a durable platelet response was similar between patients with baseline platelet counts above or below 20×10^9/L. The median duration of treatment for the 19 patients who achieved a durable platelet response was 37 weeks (range, 13 to 56 weeks).

Transfusions and Bleeding

Blood transfusions, including RBC and platelet transfusions, were given to patients either prophylactically (seven patients, 16%) or therapeutically (23 patients, 52%). Overall, 20 patients had at least one platelet transfusion, including 33%, 45%, 55%, and 44% of the patients in the 300-, 700-, 1,000-, and 1,500-μg cohorts, respectively. During the extension phase, platelet transfusions were received by a smaller proportion of patients who experienced a durable platelet response (three of 19, 16%) than those who did not (13 of 22, 59%). Platelet transfusions in responding patients were administered before the response began in two patients and after the response had ended in one patient. Twenty-three (52%) of 44 patients had at least one bleeding event. Of 73 total bleeding events, 64 were grade 1 (88%), five (7%) were grade 2, and four were $\geq$ grade 3 in severity (5%; two of hematoma and one each of cerebral hemorrhage and hematuria). Clinically significant bleeding occurred less frequently in durable responders (one patient) than nonresponders (eight patients). The incidence of bleeding events and platelet transfusions was less common among patients who achieved a durable platelet response (4.3 per 100 patient-weeks; 95% CI, 3.1 to 5.9 per 100 patient-weeks) than those who did not (39.3 per 100 patient-weeks; 95% CI, 33.5 to 45.8 per 100 patient-weeks; Fig. 3).

Safety and Adverse Events: Summary of Adverse Events

Forty-three patients (98%) reported one or more adverse events (Table 3). The most common were fatigue (27%), diarrhea (25%), and headache (21%). Serious adverse events occurred in 17 patients (39%). Adverse events leading to study withdrawal during the treatment phase occurred in one patient, for transiently increased blast counts (1,500-μg cohort); and during the extension phase occurred in two patients, for chloroma (300-μg cohort) and diarrhea (1,000-μg cohort).

Adverse events considered romiplostim-related occurred in 17 patients (39%; Table 3). Treatment-related serious adverse events occurred in five patients (11%), all of whom were in the 1,500-μg dose cohort: osteonecrosis; blast cell count increase; anemia, vertigo, and presyncope; febrile neutropenia; and thrombocytopenia. In none of the dose cohorts did more than 33% of patients experience a treatment-related adverse event; therefore, the MTD was not identified. There were four deaths. One patient in the 300-μg cohort who received romiplostim for 22 weeks experienced a cerebral hemorrhage. Another patient in the 300-μg cohort experienced a fall but did not seek medical care, and was found dead later that day. One patient in the 1,000-μg cohort who received treatment for 56 weeks died from general physical health deterioration. Lastly, a patient who received three romiplostim doses of 1,500 μg was hospitalized for multiple small hemorrhages 3 weeks after the last dose, and died 11 days later with a diagnosis of MDS. None of the deaths were considered to be related to romiplostim treatment.

Table 2. Platelet Responses

Parameter	Romiplostim (μg) 300	700	1,000	1,500
No. of patients	6	11	11	16
Platelet response during the treatment phase*				
Patients achieving a complete or major platelet response, No.	3	5	4	8
%	50	46	36	50
95% binomial CI	12 to 88	17 to 77	11 to 69	25 to 75
Baseline platelet count no./No.				
$\leq 20 \times 10^9$/L	0/2	1/4	1/4	2/6
%	0	25	25	33
$> 20 \times 10^9$/L	3/4	4/7	3/7	6/10
%	75	57	43	60
Patients achieving a complete platelet response, No.	2	3	3	6
%	33	27	27	38
95% binomial CI	4 to 78	6 to 61	6 to 61	15 to 65
Patients achieving a major platelet response, No.	1	2	1	2
%	17	18	9	13
95% binomial CI	0 to 64	2 to 52	0 to 41	2 to 38
No. of patients	6	11	11	13
Durable platelet response in patients who entered extension phase†				
Patients achieving a durable platelet response, No.	3	6	4	6
%	50	55	36	46
95% binomial CI	12 to 88	23 to 83	11 to 69	19 to 75
Baseline platelet count, no./No.				
$\leq 20 \times 10^9$/L	0/2	3/4	1/4	2/4
%	0	75	25	50
$> 20 \times 10^9$/L	3/4	3/7	3/7	4/9
%	75	43	43	44

*Using International Working Group 2000 response criteria: complete platelet response, an increase of platelet count to $> 100 \times 10^9$/L; major platelet response, an increase of absolute platelet count by $> 30 \times 10^9$/L.

†Using International Working Group 2006 response criteria: hematologic improvement in platelets for at least 8 consecutive weeks, either an absolute increase $\geq 30 \times 10^9$/L for patients with a baseline platelet count of $> 20 \times 10^9$/L, or an increase from $< 20 \times 10^9$/L to $> 20 \times 10^9$/L and by at least 100%. Platelet counts obtained within 72 hours of platelet transfusion were not evaluated for durable platelet response.

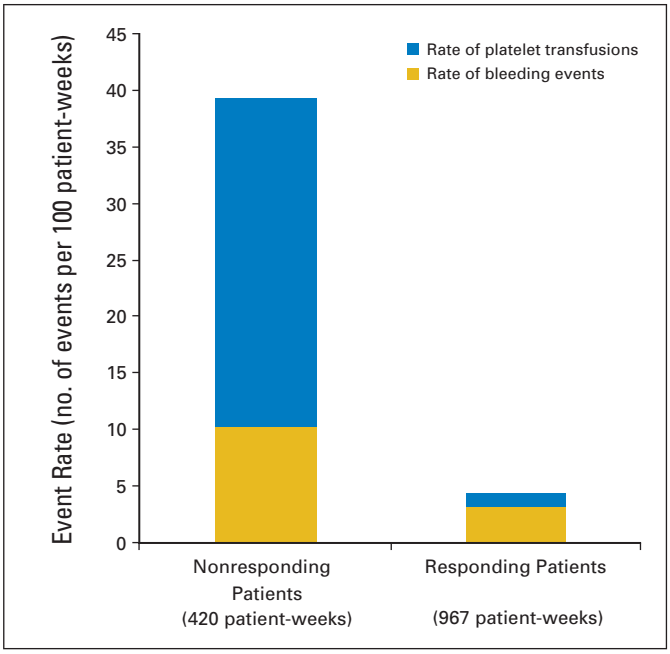

Fig 3. Rate of platelet transfusions and bleeding events in responding and nonresponding patients. All events, occurring during both the treatment and extension phases, were counted. In responding patients (n = 19) the rate of bleeding events and platelet transfusions was 4.3 per 100 patient-weeks (95% CI, 3.1 to 5.9 per 100 patient-weeks), and in nonresponding patients (n = 22) was 39.3 per 100 patient-weeks (95% CI, 33.5 to 45.8 per 100 patient-weeks).

Adverse Events of Interest

TPO mimetics may potentially increase the risk of thrombosis and bone marrow reticulin deposition. One thrombotic event was reported: a catheter-related complication in a patient receiving 1,500-μg romiplostim, which occurred at a platelet count of 255×10^9/L, was not considered serious or treatment related. Of 24 patients for whom both pretreatment and end-of-treatment or end-of-study reticulin–stained biopsies were available, the reticulin grade was increased in seven, unchanged in 10, and decreased in seven. No neutralizing antibodies to either romiplostim or endogenous TPO were seen. No patients had a reported shift to less-favorable cytogenetics from their baseline values; however, end-of-study cytogenetics were available in only 11 patients (25%).

Transient Blast Cell Increases and Progression to AML

Bone marrow evaluations revealed four cases (9%) of transiently increased blast counts. These patients received romiplostim for 3 to 8 weeks at maximum doses of 700 μg (one patient), 1,000 μg (one patient), or 1,500 μg (two patients). Blast percentages were 0%, 5%, 5%, and 3% at baseline, and following increases to more than 20% subsequently decreased within 5 weeks of romiplostim withdrawal to 8%, 6%, 7%, and 10%, respectively. No changes in cytogenetics occurred.

Two cases (5%) of AML progression occurred during the study. The first patient had a WHO classification of refractory anemia and an IPSS score of 0.5 at baseline, with 4% blasts. After receiving 300 μg romiplostim for 17 weeks the patient was diagnosed with chloroma (myeloid sarcoma). No treatment was given, and romiplostim was administered until week 31, when the chloroma was reported to have worsened, resulting in discontinuation of romiplostim. Two small subcutaneous nodules were fully excised, and pathology reports indicated that they were collections of differentiating myeloid cells. There was no recurrence of the lesions. Two weeks after the last dose of romiplostim, the central laboratory found less than 1% blasts in the bone marrow. The second patient had a WHO classification of refractory cytopenia with multilineage dysplasia and an IPSS score of 0 at baseline, with 4% blasts. The patient had previously received azacitidine as therapy for MDS. Romiplostim was administered at 1,000 μg until treatment was completed at week 55. Bone marrow blasts were 23% at week 36 and a biopsy taken 4 weeks after the last dose of romiplostim at the end-of-study visit showed 24% blasts, consistent with a diagnosis of AML. Cytogenetics remained unchanged in both patients.

Table 3. Summary of Adverse Events

Parameter	Romiplostim (μg) 300 No.	300 %	700 No.	700 %	1,000 No.	1,000 %	1,500 No.	1,500 %	All No.	All %
No. of patients	6		11		11		16		44	
Patients with any AE by grade*	6	100	11	100	11	100	15	94	43	98
3	2	33	5	46	3	27	6	38	16	36
4	2	33	2	18	1	9	3	19	8	18
5	2	33	0		1	9	1	6	4	9
Serious	2	33	3	27	2	18	10	63	17	39
Patients with any treatment-related AE by grade	0		3	27	5	46	9	56	17	39
3	0		1	9	1	9	3	19	5	11
4	0		0		0		3	19	3	7
5	0		0		0		0		0	
Serious	0		0		0		5	31	5	11
AE occurring in ≥ 10% of patients†										
Fatigue	4	67	5	46	0		3	19	12	27
Diarrhea	3	50	1	9	2	18	5	31	11	25
Headache	1	17	3	27	2	18	3	19	9	21
Edema peripheral	3	50	2	18	1	9	2	13	8	18
Hematoma	0		2	18	2	18	4	25	8	18
Back pain	1	17	3	27	3	27	1	6	8	18
Nausea	0		1	9	1	9	5	31	7	16
Contusion	2	33	1	9	1	9	3	19	7	16
Vomiting	2	33	2	18	0		2	13	6	14
Arthralgia	0		3	27	2	18	1	6	6	14
Upper respiratory tract infection	2	33	1	9	1	9	2	13	6	14
Dizziness	2	33	2	18	1	9	1	6	6	14
Pain in extremity	1	17	2	18	0		3	19	6	14
Cough	1	17	1	9	3	27	1	6	6	14
Epistaxis	1	17	1	9	3	27	1	6	6	14
Nasopharyngitis	1	17	2	18	0		2	13	5	11
Dyspnoea	1	17	2	18	0		2	13	5	11
Asthenia	1	17	1	9	2	18	1	6	5	11
Ecchymosis	2	33	1	9	2	18	0		5	11
Anorexia	1	17	3	27	0		1	6	5	11

Abbreviation: AE, adverse event.
*Events were coded according to the MedDRA Dictionary and severity was graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.
†Included events that were related and unrelated to treatment.

DISCUSSION

The results of this study indicate that romiplostim appears to be a well-tolerated treatment for thrombocytopenia in patients with lower-risk MDS. Romiplostim at doses of 300 to 1,500 μg increased median platelet counts above baseline levels during treatment for up to 1 year. Durable platelet responses were observed in almost half of the patients who continued into the extension phase of the study, independent of their baseline platelet count. Patients experiencing durable responses had fewer platelet transfusions and clinically relevant bleeding events. There were few withdrawals due to adverse events, few treatment-related serious adverse events, and no treatment-related deaths. No neutralizing antibodies to either romiplostim or endogenous TPO were reported.

Bleeding complications resulting from thrombocytopenia and platelet dysfunction are a major cause of death in patients with MDS.[5] Raising platelet counts to a level that reduces bleeding risk is a treatment goal for patients with thrombocytopenia, as reflected in response criteria within the 2006 IWG. The clinical benefit of achieving a durable platelet response was demonstrated by the reduced incidence of severe bleeding events and platelet transfusions in responding versus nonresponding patients. One fatal bleeding event occurred—a cerebral hemorrhage in a nonresponding patient.

The extent to which the severity of baseline thrombocytopenia affected patients' ability to achieve a platelet response was dependent on the response criteria used. IWG 2000 criteria were used during the treatment phase, and response rates seemed higher among patients with baseline platelet counts higher than 20×10^9/L than among patients with baseline platelet counts $\leq 20 \times 10^9$/L. The IWG adapted their criteria in 2006 to reflect clinically relevant changes in platelet counts for severely thrombocytopenic patients, and to apply rigorous standards to response durations that provide significant clinical benefit. Durable response rates in the extension study were similar between patients with baseline platelet counts above or below 20×10^9/L, indicating that romiplostim can

maintain therapeutically beneficial increases in platelet counts, even in patients with severe thrombocytopenia.

The proportion of patients achieving a platelet response per IWG 2000 or 2006 criteria appeared to be independent of the dose administered. This finding is consistent with reports that administering TPO at doses above optimal levels did not produce additional increases in platelet counts in mice.[18] No additional clinical benefit was observed by increasing the romiplostim dose to 1,000 μg and above. Based on these findings and comparisons of absolute platelet counts in each cohort, the 700-μg dose was selected for future studies.

A theoretical risk exists that TPO receptor agonists may change the natural rate of progression of MDS to AML. The c-Mpl receptor is expressed on hematopoietic cell surfaces, and a range of TPO concentrations (20 to 200 ng/mL) can stimulate certain subsets of myeloid blast cells in vitro.[19,20] Therefore, c-Mpl receptor stimulation may potentially accelerate the growth of pre-existing hematopoietic malignancies. In this study, blast cell counts were transiently increased in four patients; pretreatment blast percentages were consistent with those of the overall study population. The factors that may increase the chance of blast cell increases in romiplostim-treated patients remain to be established; however, normalization of blast cell counts after romiplostim withdrawal indicates that AML progression did not occur. Treatment with granulocyte colony-stimulating factor produces similar transient blast increases that normalize after drug withdrawal.[21] Two patients demonstrated confirmed AML progression, and the times to progression from their dates of MDS diagnosis were 0.8 and 3.2 years. Of relevance to this study population, thrombocytopenia in MDS is an independent adverse risk factor for survival,[8] and a correlation has been found between increased severity of thrombocytopenia and shorter time to AML progression.[9] The time to AML transformation for 25% of patients with platelet counts between 20 and 49 $\times$ 10^9/L was 1.3 years, compared with 3.8 years for patients with platelet counts higher than 100 $\times$ 10^9/L.[9] The potential for romiplostim to increase the risk of AML transformation could not be fully evaluated because of the lack of a placebo control. However, after more than 1 year of treatment in some patients, the incidence of disease progression remained low and within the expected range for a population of severely thrombocytopenic patients with lower-risk MDS.

Some limitations of the study should be noted. Patients who received disease-modifying therapy to render them lower risk before study entry may have a different natural history of MDS than the de novo lower-risk patients. Conclusions on the effectiveness of romiplostim are limited by the lack of a control group; however, the decreased incidence of bleeding events and platelet transfusions in responding patients suggests that romiplostim provided clinical benefit. Results from ongoing studies in larger numbers of patients will be required to better understand the long-term safety profile of romiplostim treatment in this patient population. Ongoing randomized trials and future combination studies will optimize the dose schedules of romiplostim and define its precise therapeutic role in MDS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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