Safety and efficacy of romiplostim in splenectomized and nonsplenectomized patients with primary immune thrombocytopenia

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Haematologica 2017
Volume 102(8):1342-1351

ABSTRACT

Primary immune thrombocytopenia is an autoimmune disorder characterized by increased platelet destruction and insufficient platelet production without another identified underlying disorder. Splenectomy may alter responsiveness to treatment and/or increase the risk of thrombosis, infection, and pulmonary hypertension. The analysis herein evaluated the safety and efficacy of the thrombopoietin receptor agonist romiplostim in splenectomized and nonsplenectomized adults with primary immune thrombocytopenia. Data were pooled across 13 completed clinical studies in adults with immune thrombocytopenia from 2002-2014. Adverse event rates were adjusted for time of exposure. Results were considered different when 95% confidence intervals were non-overlapping. Safety was analyzed for 1111 patients (395 splenectomized; 716 nonsplenectomized) who received romiplostim or control (placebo or standard of care). At baseline, splenectomized patients had a longer median duration of immune thrombocytopenia and a lower median platelet count, as well as a higher proportion with >3 prior immune thrombocytopenia treatments *versus* nonsplenectomized patients. In each treatment group, splenectomized patients used rescue medications more often than nonsplenectomized patients. Platelet response rates (≥50x10^9/L) for romiplostim were 82% (310/376) for splenectomized and 91% (592/648) for nonsplenectomized patients (P<0.001 by Cochran-Mantel-Haenszel test). Platelet responses were stable over time in both subgroups. Exposure-adjusted adverse event rates were higher for control *versus* romiplostim for both splenectomized (1857 *versus* 1226 per 100 patient-years) and nonsplenectomized patients (1052 *versus* 852 per 100 patient-years). In conclusion, responses to romiplostim were seen in both splenectomized and nonsplenectomized patients, and romiplostim was not associated with an increase in the risk of adverse events in splenectomized patients. *clinicaltrials.gov Identifier: 00111475(A)(B), 00117143, 00305435, 01143038, 00102323, 00102336, 00415532, 00603642, 00508820, 00907478, 00116688, and 00440037.*

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Received: December 15, 2016.
Accepted: April 12, 2017.
Pre-published: April 14, 2017.

doi:10.3324/haematol.2016.161968

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/102/8/1342

Introduction

In primary immune thrombocytopenia (ITP), increased platelet destruction and suboptimal platelet production result in low platelet counts, with bleeding symptoms that range from minimal to severe.[1,2] The thrombopoietin (TPO) receptor agonist romiplostim stimulates platelet production.[3] Romiplostim is approved in The USA for the treatment of chronic ITP in adults who have had an insufficient

Table 1. Studies included in this analysis.

Study identifier*	Study design	Control	No. Splenectomized / Nonsplenectomized**	Reference
Parent studies				
00111475(A)	Phase 1 dose-finding***	None	19/5	6
00111475(B)	Phase 2 dose-finding***	Placebo	14/7	6
00117143	Phase 2 dose-finding***	None	13/3	7
00305435	Phase 2 dose-finding***	None	3/9	8
01143038	Phase 2	None	0/75	9
00102323	Phase 3	Placebo	63/0	10
00102336	Phase 3	Placebo	0/62	10
00415532	Phase 3	SOC	0/229	11
00603642	Phase 3	Placebo	15/19	12
00508820	Phase 3	None	208/198	13
00907478	Phase 4	None	60/109	14
Extension studies				
00116688	Open-label extension	None	94/197	15
00440037	Open-label extension	None	17/27	16

*Registry number from clinicaltrials.gov Identifier. **Number of adults who received study treatment. The total of 335 patients in the 2 open-label extension studies previously participated in a parent study and are counted twice in the table. If a patient received control in the parent study and romiplostim in the open-label extension study, data from the parent study were included in the control group and data from the extension study were included in the romiplostim group. ***Dose-finding studies were not included in efficacy analyses because they used off-label doses of romiplostim. SOC: standard of care.

response to corticosteroids, intravenous immunoglobulins (IVIGs), or splenectomy,[4] and in Europe for adults with chronic ITP who are refractory to other treatments (e.g., corticosteroids, IVIGs).[5] Across 13 clinical studies of romiplostim in patients with primary ITP,[6-16] romiplostim improved platelet counts, reduced bleeding, and reduced the use of concomitant medications compared with placebo or standard of care (SOC). The frequencies of on-study splenectomy and serious adverse events (AEs) were lower in patients treated with romiplostim compared with SOC.[11]

The spleen is an important site of antigen presentation, antibody production, and perpetuation of the autoimmune response in patients with ITP.[17-19] Splenectomy, which reduces clearance of antibody-coated platelets and may attenuate antibody production, induces a complete clinical remission in approximately two-thirds of patients.[20-22] Treatment guidelines include splenectomy as a second-line therapy for adults with ITP (after first-line therapy with corticosteroids, intravenous anti-D, or IVIG),[1,2] based on extensive clinical experience and evidence to support the benefit/risk profile for splenectomy. However, approximately one-third of patients relapse or fail to respond to splenectomy and may require additional therapy.[20,21]

The impact of splenectomy on the safety and efficacy of treatment with romiplostim is not well described.[23] Splenectomized patients were enrolled in some of the romiplostim ITP studies, but the benefits and risks in this subpopulation were not specifically addressed in previous pooled analyses.[24,25] One concern about inducing sustained responses in patients with a prior splenectomy involves the potential to increase the risk of thrombosis, including portal and mesenteric venous thrombosis in the perioperative period after splenectomy in general[26,27] and specifically in patients with ITP.[28,29] The latter is complicated somewhat by the finding that ITP itself carries a slightly increased risk of thrombosis.[28-32] Increased thrombosis after splenectomy may be associated with the eventual development of pulmonary hypertension,[26,33-35] or atherosclerosis.[26] The mechanism by which splenectomy predisposes to thromboembolism is unclear but, in theory, a sustained increase in platelet count could contribute to this risk.[30]

Splenectomy also increases the risk of infection, especially overwhelming sepsis caused primarily by encapsulated bacteria.[30,36] Postsplenectomy infection is more common in the first 2 years after splenectomy. However, infection remains a lifelong risk because the spleen enhances clearance of antibody- and complement-coated particulate antigens, and it produces opsonins and immunologic memory cells.[30,37,38] The long-term risk of postsplenectomy infection may be reduced by vaccination or prophylactic antibiotics.[30,38]

Therefore, on the one hand, splenectomy removes a major site of platelet sequestration,[39,40] which may improve responsiveness to stimulation of platelet production by romiplostim. On the other hand, patients who have undergone splenectomy may comprise a subset of patients with more protracted, severe, and unresponsive disease who may also prove to be refractory to romiplostim and may be at greater risk of thrombosis and infection. This analysis was conducted to evaluate the safety and efficacy of romiplostim in splenectomized and nonsplenectomized adults with primary ITP.

Methods

Patients and studies

Methods for the pooled analyses were reported previously.[24,25] Data were analyzed from 13 studies of romiplostim in adults with

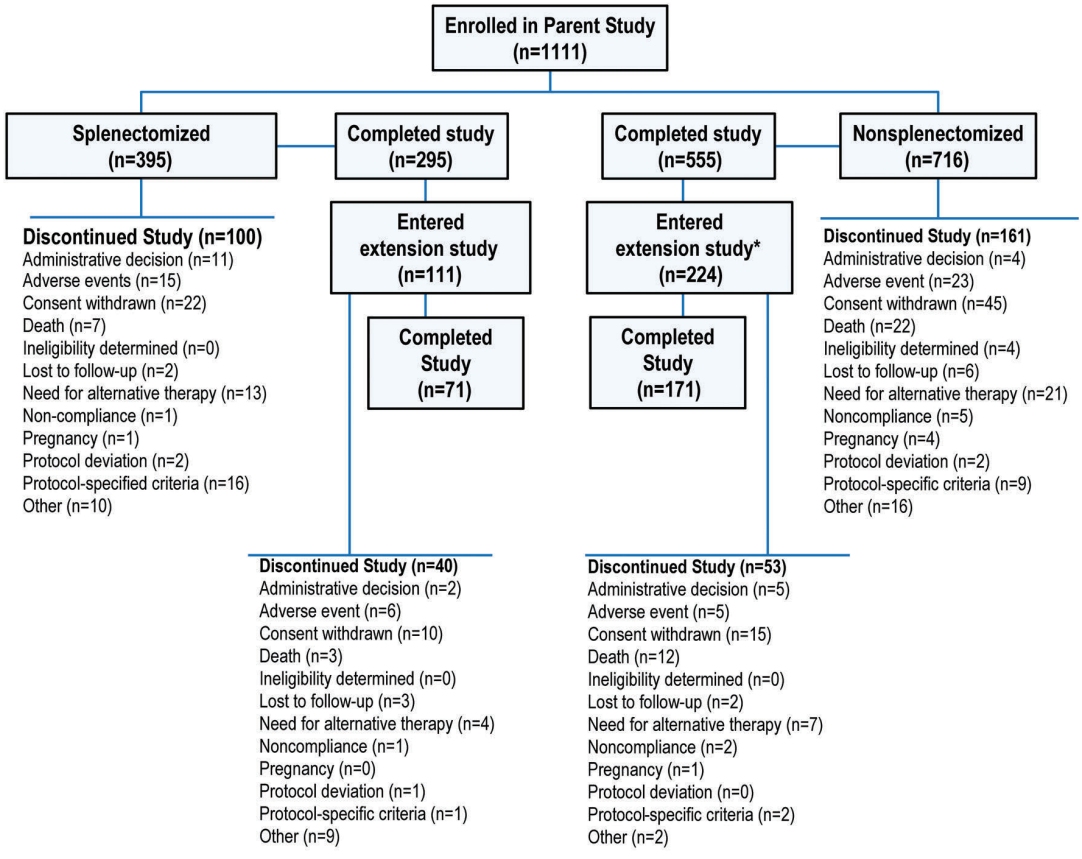

Figure 1. Patient disposition. *One nonsplenectomized patient entered the extension study but did not receive romiplostim; the data from this patient were excluded.

primary ITP conducted between 2002 and 2014, including 5 controlled studies, 6 single-arm studies, and 2 open-label extension studies (Table 1).[6-16] These studies were conducted in compliance with regulatory obligations, including institutional review board and informed consent regulations.

Patients were diagnosed with primary ITP per American Society of Hematology guidelines.[41] Patients received subcutaneous romiplostim, placebo, or SOC, along with concomitant or rescue medications (such as IVIG, but excluding other TPO mimetics and investigational products) as required and allowed per study. Platelet counts were targeted to be in the range of 50-200x10^9/L. In some earlier studies, the dose of romiplostim was adjusted between 1 and 15 μg/kg/week;[10,13] in all other studies, the dose was adjusted between 1 and 10 μg/kg/week.

Assessments and statistical methods

Measurements of platelet counts and use of other ITP treatments were documented at each visit. AE assessments were based on symptoms at any time during the study. Investigators evaluated AEs as to causality and severity (1=mild to 5=fatal). A serious AE was fatal, life-threatening, required (or prolonged) hospitalization, resulted in significant disability/incapacity, or was another significant complication. Amgen monitored serious AEs on an ongoing basis, and all AEs were reviewed quarterly. Other safety data, including laboratory values, were reviewed on an *ad hoc* basis for individual patients and on an ongoing basis for emerging trends. Bone marrow findings from a long-term study of bone marrow morphology were reported separately;[14] other data from that study not related to bone marrow findings were included in this pooled analysis. Bone marrow findings from AE reports in all other studies and available bone marrow biopsy results from 1 of the open-label extension studies[15] were reported using the modified Bauermeister grading scale. The total number of bone marrow biopsies performed was unknown because results were only reported if the outcome was considered to be an AE, with the exception of the extension study noted above.

Data from the placebo and SOC treatment arms were pooled. Unless otherwise indicated, results were adjusted for study duration and reported as events per 100 patient-years (calculated as 100x the number of events/patient-year), in order to reflect the unequal study duration between patients who received romiplostim and those who received placebo/SOC. When patients were enrolled in 2 consecutive studies, data from the parent and extension studies were combined. For patients who initially received placebo or SOC and then romiplostim, data prior to the first dose of romiplostim were included in the placebo/SOC group, and data beginning on the day the first dose of romiplostim was given were included in the romiplostim group, regardless of any subsequent change in treatment. Analyses were performed separately for patients who were splenectomized or nonsplenectomized before the parent study. Comparisons between splenectomized and nonsplenectomized patients included prespecified tests for platelet responses (*P*-values from Cochran-Mantel-Haenszel tests) and *ad hoc* analysis for other endpoints (95% confidence intervals).

Table 2. Patient characteristics.

Characteristic	Splenectomized (N=395)	Nonsplenectomized (N=716)
Age, years, median (95% CI)	52.0 (50.0, 55.0)	53.0 (52.0, 56.0)
Female, n (%)	254 (64.3)	431 (60.2)
Years since ITP diagnosis, median (95% CI)	8.7 (7.7, 9.7)	1.6 (1.4, 2.0)
>3 prior ITP therapies, n (%) (95% CI)	150 (38.0) (33.2, 42.8)	84 (11.7) (9.4, 14.1)
Baseline platelet count x10^9/L, median (95% CI)	14.0 (12.0, 15.3)	19.3 (18.0, 21.0)

CI: confidence interval; ITP: immune thrombocytopenia.

Table 3. Exposure-adjusted rates of AEs per 100 pt-yr (95% CI).

AE category	Romiplostim*		Placebo/SOC	
	Splenectomized N=391** (702.0 pt-yr)	Nonsplenectomized N=655** (1129.7 pt-yr)	Splenectomized N=27** (11.2 pt-yr)	Nonsplenectomized N=106** (97.7 pt-yr)
Any AE	1226 (1201, 1253)	852 (835, 869)	1857 (1613, 2127)	1052 (989, 1119)
Any serious AE	68.1 (62.1, 74.5)	44.1 (40.3, 48.1)	133.9 (75.0, 220.9)	94.2 (75.9, 115.5)
Any fatal AE	1.6 (0.8, 2.8)	2.7 (1.9, 3.9)	26.8 (5.5, 78.3)	5.1 (1.7, 11.9)
Any treatment-related AE	123.1 (115.0, 131.6)	82.1 (76.9, 87.6)	133.9 (75.0, 220.9)	155.6 (131.8, 182.4)
Any treatment-related serious AE	9.3 (7.1, 11.8)	5.2 (4.0, 6.7)	0.0 (0.0, 32.9)	18.4 (10.9, 29.1)

*Any event reported after the first dose of romiplostim. **Of the 1111 patients, 978 (368 splenectomized, 610 nonsplenectomized) received only romiplostim, 65 (4 splenectomized, 61 nonsplenectomized) received only placebo/SOC, and 68 (23 splenectomized, 45 nonsplenectomized) received placebo/SOC in a parent study and romiplostim in an open-label extension study. Safety outcomes for the latter 68 patients were analyzed in both groups: events before the switch were attributed to placebo/SOC and events after the switch were attributed to romiplostim. AE: adverse event; CI: confidence interval; pt-yr: patient-year(s); SOC: standard of care.

Results

Studies and patients

Results from a total of 1111 patients enrolled in a parent study were analyzed, including 395 who were splenectomized and 716 who were nonsplenectomized (Figure 1). Of the 1111 patients, 978 (368 splenectomized, 610 nonsplenectomized) received only romiplostim, 65 (4 splenectomized, 61 nonsplenectomized) received only placebo/SOC, and 68 (23 splenectomized, 45 nonsplenectomized) received placebo/SOC in a parent study and romiplostim in an open-label extension study. Safety outcomes for the latter 68 patients were analyzed in both groups; events before the switch were attributed to placebo/SOC and events after the switch were attributed to romiplostim. Thus, the safety analyses included data for 1046 patients in the romiplostim group (391 splenectomized and 655 nonsplenectomized) and 133 in the placebo/SOC group (27 splenectomized and 106 nonsplenectomized).

A similar proportion of splenectomized and nonsplenectomized patients discontinued the parent study. Median age and sex were similar between the two cohorts, but splenectomized patients had a longer duration of ITP and lower baseline platelet counts *versus* nonsplenectomized patients, and a higher proportion of splenectomized patients had received more than 3 prior ITP treatments (Table 2).

Efficacy

Response based on platelet count was analyzed in 1024 patients treated with romiplostim (376 splenectomized; 648 nonsplenectomized); 22 patients in dose-finding studies received off-label doses of romiplostim and were not included in efficacy analyses. Using a target platelet count of 50-200x10^9/L, median platelet counts were maintained within the target range in most splenectomized and nonsplenectomized patients (Figure 2A). A platelet response (at least 1 platelet count ≥50x10^9/L without rescue medication use in the previous 4 weeks) was attained in 82% of splenectomized patients and 91% of nonsplenectomized patients (Figure 2B). A sustained platelet response was attained in 68% of splenectomized patients and 80% of nonsplenectomized patients (Figure 2B). For this analysis, a sustained platelet response was defined as platelet counts ≥50x10^9/L for 9 out of 12 weeks (75% of weekly assessments), with no use of rescue medication during the 4 weeks prior to each qualifying platelet count. The qualifying criterion for sustained response was any 12-week interval that started with a platelet count ≥50x10^9/L. Patients with more than 1 sustained platelet response were counted only once in the analysis. Response rates and sustained response rates were lower in splenectomized patients than in nonsplenectomized patients (P<0.001 by Cochran-Mantel-Haenszel test both for any platelet response and for sustained platelet response).

The use of rescue medication was higher in splenectomized than in nonsplenectomized patients within each treatment group (Figure 2C). In both splenectomized and nonsplenectomized patients, the use of corticosteroids, IVIG, anti-D, and rituximab decreased from baseline with long-term treatment and follow up (Figure 3).

Exposure

Splenectomized patients received romiplostim for up to 281 weeks and nonsplenectomized patients for up to 283 weeks, with mean (standard deviation [SD]) treatment durations of 87.3 (75.5) and 82.2 (60.0) weeks, respectively. The mean (SD) dose of romiplostim used most frequently was 4.9 (4.0) μg/kg for splenectomized patients

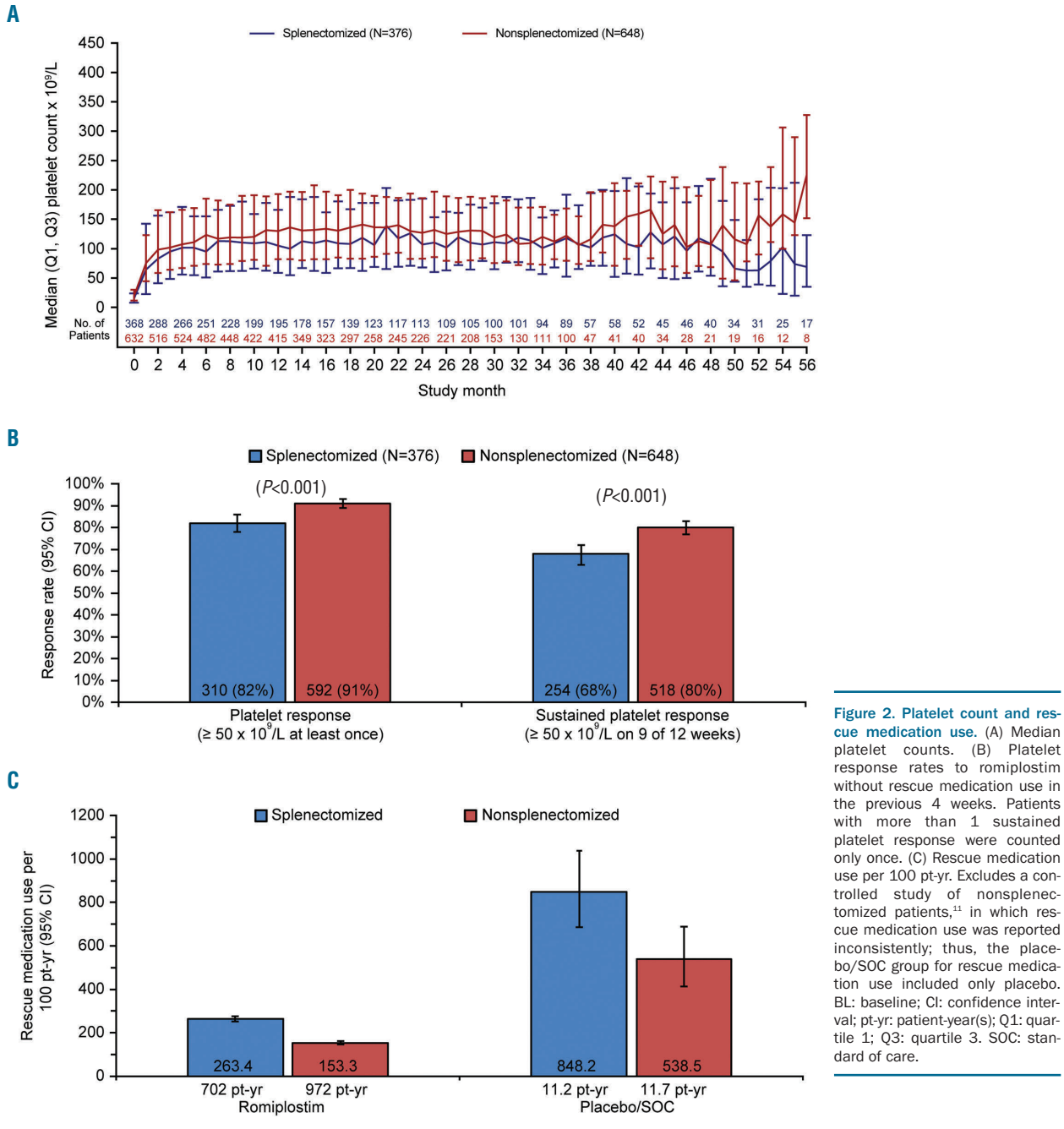

Figure 2. Platelet count and rescue medication use. (A) Median platelet counts. (B) Platelet response rates to romiplostim without rescue medication use in the previous 4 weeks. Patients with more than 1 sustained platelet response were counted only once. (C) Rescue medication use per 100 pt-yr. Excludes a controlled study of nonsplenectomized patients,[11] in which rescue medication use was reported inconsistently; thus, the placebo/SOC group for rescue medication use included only placebo. BL: baseline; CI: confidence interval; pt-yr: patient-year(s); Q1: quartile 1; Q3: quartile 3. SOC: standard of care.

and 4.4 (3.4) μg/kg for nonsplenectomized patients (Figure 4A). Mean doses of romiplostim during >50 months of treatment were also similar comparing splenectomized to nonsplenectomized patients (Figure 4B). Total exposure to romiplostim was 702.0 patient years in splenectomized patients and 1129.7 patient-years in nonsplenectomized patients. Total exposure to placebo/SOC was 11.2 patient-years in splenectomized patients and 97.7 patient-years in nonsplenectomized patients.

Safety

In each treatment group, exposure-adjusted rates of AEs, serious AEs, treatment-related AEs, and treatment-related serious AEs were higher among splenectomized *versus* nonsplenectomized patients (Table 3). The confidence intervals around the rates for splenectomized and nonsplenectomized patients did not overlap for AE rates and serious AE rates in either the romiplostim group or in the placebo/SOC group.

Exposure-adjusted rates of AEs and serious AEs (Table 3) were lower with romiplostim treatment *versus* treatment with placebo/SOC in both splenectomized and nonsplenectomized patients. For each comparison, the confidence intervals around the rates for romiplostim and placebo/SOC did not overlap, showing a significant reduction in the event rates. The rate ratio for exposure-adjusted AE rates for romiplostim compared with placebo/SOC was 0.81 among nonsplenectomized patients (852 *versus*

Table 4. Rates of AEs of interest per 100 pt-yr (95% CI).

AE of interest	Romiplostim*		Placebo/SOC	
	Splenectomized N=391** (702.0 pt-yr)	Nonsplenectomized N=655** (1129.7 pt-yr)	Splenectomized N=27** (11.2 pt-yr)	Nonsplenectomized N=106** (97.7 pt-yr)
Hemorrhagic	266.1 (254.2, 278.4)	140.8 (134.0, 147.9)	482.1 (362.2, 629.1)	238.5 (208.8, 271.2)
Thrombotic	6.3 (4.6, 8.4)	4.6 (3.4, 6.0)	8.9 (0.2, 49.7)	5.1 (1.7, 11.9)
Reticulin***	0.4 (0.0, 1.3) (N=331; 560.6 pt-yr)	0.6 (0.2, 1.3) (N=546; 866.7 pt-yr)	0.0 (0.0, 32.9)	0.0 (0.0, 3.8)
Any infection	156.7 (147.6, 166.2)	124.8 (118.4, 131.5)	196.4 (123.1, 297.4)	112.6 (92.5, 135.7)
Possible opportunistic infection****	8.7 (6.6, 11.2)	4.5 (3.4, 5.9)	0.0 (0.0, 32.9)	5.1 (1.7, 11.9)
Systemic infection****	2.1 (1.2, 3.5)	0.4 (0.1, 0.9)	0.0 (0.0, 32.9)	3.1 (0.6, 9.0)

*Any event reported after the first dose of romiplostim. **Of the 1111 patients, 978 (368 splenectomized, 610 nonsplenectomized) received only romiplostim, 65 (4 splenectomized, 61 nonsplenectomized) received only placebo/SOC, and 68 (23 splenectomized, 45 nonsplenectomized) received placebo/SOC in a parent study and romiplostim in an open-label extension study. Safety outcomes for the latter 68 patients were analyzed in both groups: events before the switch were attributed to placebo/SOC and events after the switch were attributed to romiplostim. ***AEs reported as bone marrow reticulin fibrosis, myelofibrosis, or reticulin increase across 12 studies; excluded 1 single-arm romiplostim study of immune thrombocytopenia specifically designed for bone marrow assessment (reported separately[14]). ****Reported terms for infection AEs were reviewed to identify possible opportunistic infections and systemic infections (*Online Supplementary Table S3*). AE: adverse event; CI: confidence interval; SOC: standard of care; pt-yr: patient-year(s).

1052 per 100 patient-years) and 0.66 among splenectomized patients (1226 *versus* 1857 per 100 patient-years). Exposure-adjusted rates of serious AEs in the romiplostim group were 53% lower than in the placebo/SOC group among nonsplenectomized patients (44.1 *versus* 94.2 per 100 patient-years) and 49% lower among splenectomized patients (68.1 *versus* 133.9 per 100 patient-years). The exposure-adjusted rate of any serious AE tended to be highest among splenectomized patients in the placebo/SOC group, followed in turn by nonsplenectomized patients in the placebo/SOC group, splenectomized patients in the romiplostim group, and nonsplenectomized patients in the romiplostim group. The relatively low number of fatal AEs made comparisons difficult.

Several prespecified AEs of interest were analyzed separately (Table 4). Splenectomized patients had a higher incidence of bleeding than nonsplenectomized patients within each treatment group. However, the incidence of bleeding was lower in the romiplostim group than in the placebo/SOC group in both cohorts. AE rates for infections were similar between the romiplostim and placebo/SOC groups, with a small increase in infections in splenectomized patients in each treatment group. Rates of AEs reported as bone marrow reticulin fibrosis, myelofibrosis, or reticulin increase were too small for meaningful comparisons between treatment groups or across subgroups. The overall rate of any thrombotic AE was similar between the romiplostim and placebo/SOC groups and similar between splenectomized and nonsplenectomized patients within each treatment group.

Types of thrombotic AEs (*Online Supplementary Table S1*) were also similar between treatment groups and between splenectomized and nonsplenectomized patients within each treatment group. The most commonly reported thrombotic AEs in the romiplostim and placebo/SOC groups were deep vein thrombosis (1.0 *versus* 0.9 events per 100 patient-years) and pulmonary embolism (0.8 *versus* 0.9 events per 100 patient-years). The median platelet count at the last measurement before a thrombotic AE was 150.0x10^9/L in patients who received romiplostim and 52.5x10^9/L in patients who received only placebo/SOC, and the platelet counts before a thrombotic event were similar between splenectomized and nonsplenectomized patients in the romiplostim group. The percentage of time that patients in the romiplostim group had a platelet count of 50x10^9/L or greater, or 200x10^9/L or greater, was similar between patients with or without thrombotic AEs (*Online Supplementary Table S2*).

Neutralizing antibodies to romiplostim were reported for 6 patients: 2 before romiplostim treatment and 4 after treatment was initiated. All 6 patients had a platelet response and a sustained platelet response, and none lost response to romiplostim following the detection of neutralizing antibodies.

Discussion

In this analysis of 1111 patients across 13 completed clinical studies of the TPO receptor agonist romiplostim, more than 1 in 3 patients underwent splenectomy before they entered the parent study. Platelet response rates following treatment with romiplostim were high in both splenectomized and nonsplenectomized patients, and median platelet counts were generally maintained in the target range with long-term romiplostim treatment in both populations. The observed response rate was higher in nonsplenectomized patients than in splenectomized patients. A sustained platelet response for 9 out of 12 weeks was achieved by 68% of splenectomized and 80% of nonsplenectomized patients given romiplostim in this pooled analysis. In 2 pivotal phase 3 studies, 38% of splenectomized and 61% of nonsplenectomized patients given romiplostim achieved durable platelet responses.[10] In those studies, a durable platelet response was defined as platelet counts ≥50x10^9/L for ≥6 of the last 8 weeks. Although the same ratio (75% of the weekly assessments) was used to define sustained platelet responses in this pooled analysis, the start of the 12-week interval was based on a platelet count of ≥50x10^9/L. Thus, the pivotal studies examined the proportion of patients who achieved durable platelet responses during a specific 8 week interval after dose stabilization, while this analysis examined the

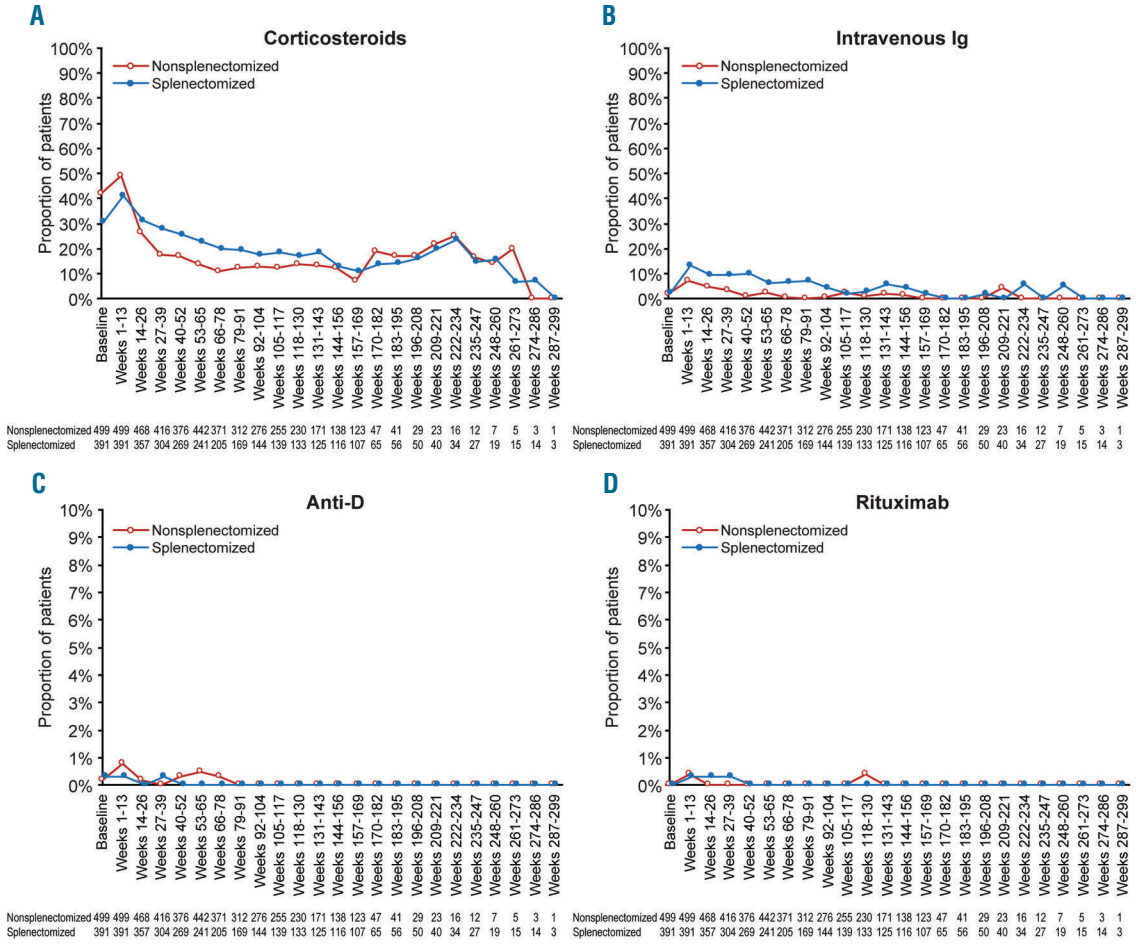

Figure 3. Use of other ITP medications in the romiplostim group: prevalence by postbaseline quarter. (A) Corticosteroids. (B) IVIG; (C) Anti-D; (D) Rituximab. Ig: immunoglobulin.

proportion of patients who sustained the response over any 12-week interval that began with a platelet response.

Interpretation of these results is complicated by the fact that the efficacy analysis pooled data across 9 studies (4 dose-finding studies used off-label doses of romiplostim and were not included in the efficacy analyses), and the splenectomized and nonsplenectomized patients were not balanced for other baseline characteristics. Splenectomized patients had more severe disease at baseline, as shown by the longer duration of ITP, a higher proportion that had used more than 3 prior ITP treatments, and a lower baseline platelet count at study entry compared with nonsplenectomized patients. The timing of splenectomy relative to other prior treatments was uncertain. Therefore, patients might have undergone splenectomy as second-line therapy or after multiple lines of therapy had failed.[1,2,41] Although the platelet responses to prior treatments were not recorded in these studies, the fact that 38% of splenectomized patients and 12% of nonsplenectomized patients received more than 3 prior lines of therapy suggests that the splenectomized patients in this analysis included more patients with treatment-resistant ITP. Exposure-adjusted rates of AEs and serious AEs were lower in the romiplostim group than in the placebo/SOC group. The difference in AE rates between the treatment groups was greater among splenectomized patients than among nonsplenectomized patients. Specifically, although splenectomized patients appeared to have more severe disease than nonsplenectomized patients at baseline, the responses to romiplostim were similar between the cohorts. Moreover, treatment with romiplostim was associated with a reduction of approximately 70% in the use of rescue medication compared with the placebo/SOC group in both splenectomized and nonsplenectomized patients. This reduction appeared to occur after initial dose titration for romiplostim, based on analyses of ITP medication use over time. The substantially greater use of concomitant medications in the placebo/SOC group may have contributed to the higher rates of AEs and serious AEs compared with patients treated with romiplostim. Notwithstanding the higher rate of AEs in splenectomized patients, the rate of serious AEs among this cohort who were treated with romiplostim was lower than that in nonsplenectomized patients in the placebo/SOC group. Thus, treatment had a greater impact on reducing the rate of serious AEs than did a prior history

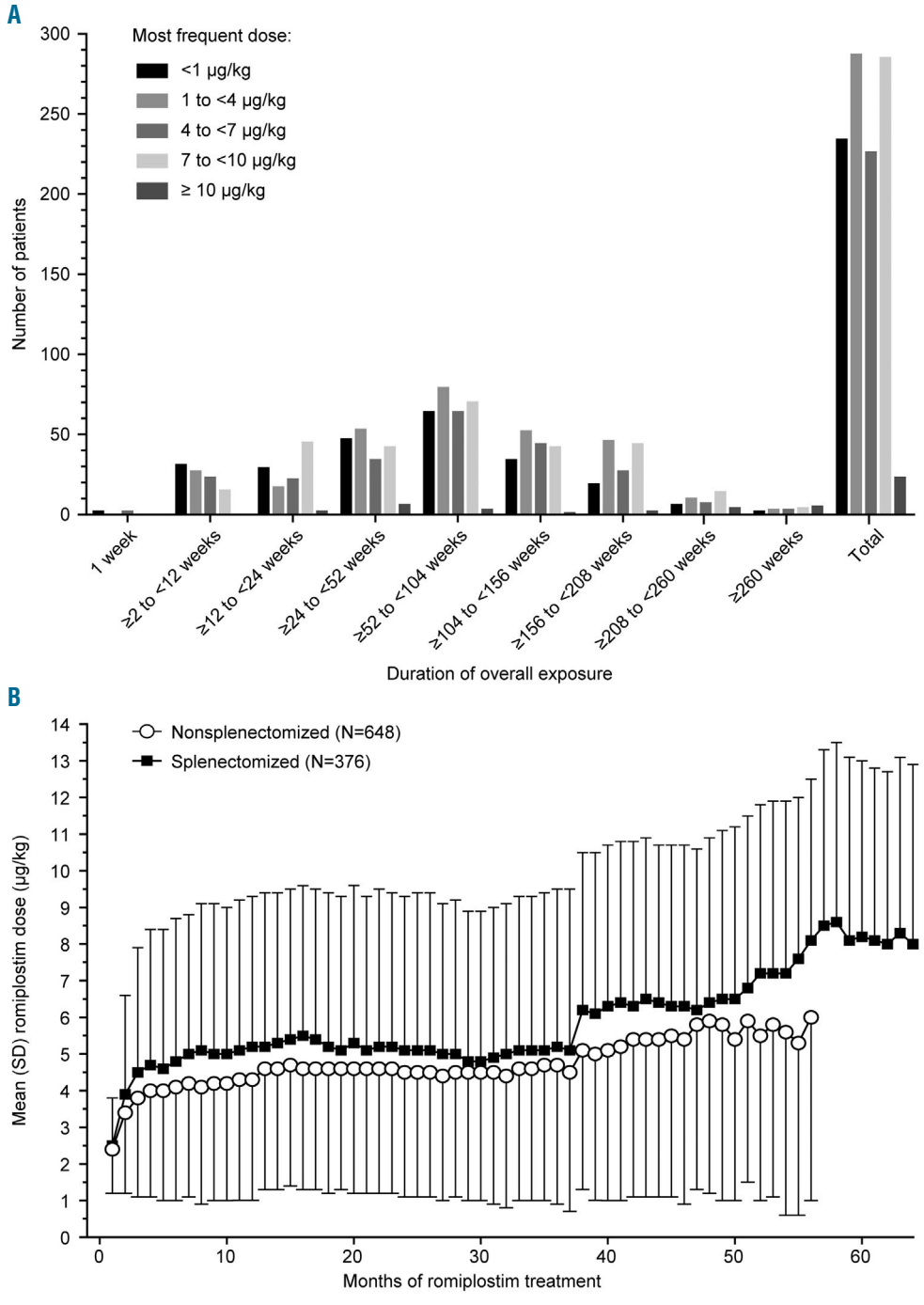

Figure 4. Romiplostim dosing. (A) Most frequent romiplostim dose. (B) Romiplostim dose over time by splenectomy status. SD: standard deviation.

of splenectomy. No new safety issues or major increases in AEs were seen among romiplostim-treated splenectomized patients compared with romiplostim-treated nonsplenectomized patients in this analysis, which included the examination of specific AEs such as bleeding, infection, thrombosis, and bone marrow fibrosis. Previous research has shown that splenectomized patients have approximately a 2-fold to 4-fold greater risk of thrombotic events than nonsplenectomized patients,[26,27] and the risk may remain elevated more than 1 year after splenectomy.[27] In this analysis, patients with a prior history of thrombotic events were excluded from some of the studies but were permitted to enroll in other studies.[25] Therefore, we cannot speculate on how many patients with prior thrombotic events were not enrolled in these studies, which could have influenced the risk of subsequent thrombotic events after initiation of romiplostim or placebo/SOC treatment.

Rates of bone marrow reticulin fibrosis, myelofibrosis, or reticulin AEs were too low for meaningful comparisons between the splenectomized and nonsplenectomized patients, or between the romiplostim and placebo/SOC groups, but no worrisome signals were observed. These analyses were limited by the fact that in most of the stud-

ies, bone marrow data were only collected for patients with a documented bone marrow AE. Additionally, the actual time at which bone marrow AEs occurred could not be evaluated; only the time of detection by bone marrow biopsy was known. One of the studies included in this pooled analysis was a single-arm study that was designed to evaluate bone marrow findings from biopsies 1, 2, or 3 years after initiation of treatment with romiplostim. A separate publication of those findings[14] showed that bone marrow changes were observed in a small proportion of patients who received long-term romiplostim treatment, including 3 out of 60 splenectomized patients and 6 out of 109 nonsplenectomized patients.

Several limitations of this pooled analysis should be noted. First, comparisons of efficacy and safety between splenectomized and nonsplenectomized patients were not among the planned analyses within the individual romiplostim studies. Some of the phase 3 studies enrolled only splenectomized patients or only nonsplenectomized patients; other studies enrolled both splenectomized and nonsplenectomized patients. The studies that enrolled both splenectomized and nonsplenectomized patients did not collect data for splenectomy during the study, which made it impossible to examine splenectomy rates in the romiplostim and placebo/SOC groups. In a 52-week study that was designed to address this question in nonsplenectomized patients, the rates of splenectomy on-study were significantly lower for romiplostim than SOC (9% *versus* 36%).[11] Second, investigators were not asked to report if an AE was related to prior splenectomy, so it was not possible to confirm the relatedness of splenectomy to safety outcomes. Third, comparisons between the romiplostim and placebo/SOC groups were limited by the differences in exposure to study treatment in each group. Eight out of 13 studies in this pooled analysis were single-arm evaluations of romiplostim, including 2 long-term open-label extension studies. Consequently, the sample sizes in this pooled analysis were much larger for romiplostim than for placebo/SOC and the total exposure to placebo/SOC was limited to 6 months or less for individual patients, whereas exposure to romiplostim could continue for several years. To address these discrepancies, analyses of AEs and rescue medication use were based on exposure-adjusted rates. After subdividing the population by treatment and splenectomy status, total exposure to placebo/SOC was only 11.2 patient-years in splenectomized patients and 97.7 patient-years in nonsplenectomized patients, *versus* exposure to romiplostim of 702.0 and 1129.7 patient-years, respectively. For the patients who received placebo/SOC in a controlled study and later received romiplostim in an extension study, efficacy and safety outcomes after the first dose of romiplostim were considered to be related to that treatment, but it is possible that SOC treatment could have impacted subsequent efficacy or safety outcomes. Fourth, the use of medications prior to study entry could have impacted efficacy and safety during the studies, but one of the pivotal studies (approximately 40% of patients in the analysis) did not collect information on prior medications. Moreover, in the other studies the only information available was whether a patient had received a medication previously, without details on the nature, intensity, or duration of prior treatment. Lastly, patients were permitted to receive rescue treatment such as IVIG, but not other investigational products or other TPO mimetics, which complicated the interpretation of platelet responses. Notwithstanding these limitations, the analyses reported herein address an important data gap regarding the safety and efficacy of romiplostim in splenectomized patients for whom therapeutic options are more limited.[23]

In conclusion, this pooled analysis of data from 13 completed studies showed that romiplostim has a favorable safety profile, regardless of splenectomy status before treatment with romiplostim. Long-term treatment with romiplostim maintained platelet counts in the target range in both splenectomized and nonsplenectomized patients, and no new safety signal emerged. Importantly, romiplostim did not increase the risk of thromboembolic events in splenectomized patients compared to placebo/SOC. Based on this *post hoc* analysis, romiplostim appears to be a treatment option for patients with ITP with or without a history of failed splenectomy.

Funding

This research, including both the original studies and the pooled analysis, was funded by Amgen Inc.

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