Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial

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Summary

Background Chronic immune thrombocytopenic purpura (ITP) is characterised by accelerated platelet destruction and decreased platelet production. Short-term administration of the thrombopoiesis-stimulating protein, romiplostim, has been shown to increase platelet counts in most patients with chronic ITP. We assessed the long-term administration of romiplostim in splenectomised and non-splenectomised patients with ITP.

Methods In two parallel trials, 63 splenectomised and 62 non-splenectomised patients with ITP and a mean of three platelet counts 30×10⁹/L or less were randomly assigned 2:1 to subcutaneous injections of romiplostim (n=42 in splenectomised study and n=41 in non-splenectomised study) or placebo (n=21 in both studies) every week for 24 weeks. Doses of study drug were adjusted to maintain platelet counts of 50×10⁹/L to 200×10⁹/L. The primary objectives were to assess the efficacy of romiplostim as measured by a durable platelet response (platelet count ≥50×10⁹/L during 6 or more of the last 8 weeks of treatment) and treatment safety. Analysis was per protocol. These studies are registered with ClinicalTrials.gov, numbers NCT00102323 and NCT00102336.

Findings A durable platelet response was achieved by 16 of 42 splenectomised patients given romplostim versus none of 21 given placebo (difference in proportion of patients responding 38% [95% CI 23·4–52·8], p=0·0013), and by 25 of 41 non-splenectomised patients given romplostim versus one of 21 given placebo (56% [38·7–73·7], p<0·0001). The overall platelet response rate (either durable or transient platelet response) was noted in 88% (36/41) of non-splenectomised and 79% (33/42) of splenectomised patients given romiplostim compared with 14% (three of 21) of non-splenectomised and no splenectomised patients given placebo (p<0·0001). Patients given romiplostim achieved platelet counts of 50×10⁹/L or more on a mean of 13·8 (SE 0·9) weeks (mean 12·3 [1·2] weeks in splenectomised group *vs* 15·2 [1·2] weeks in non-splenectomised group) compared with 0·8 (0·4) weeks for those given placebo (0·2 [0·1] weeks *vs* 1·3 [0·8] weeks). 87% (20/23) of patients given romiplostim (12/12 splenectomised and eight of 11 non-splenectomised patients) reduced or discontinued concurrent therapy compared with 38% (six of 16) of those given placebo (one of six splenectomised and five of ten non-splenectomised patients). Adverse events were much the same in patients given romiplostim and placebo. No antibodies against romiplostim or thrombopoietin were detected.

Interpretation Romiplostim was well tolerated, and increased and maintained platelet counts in splenectomised and non-splenectomised patients with ITP. Many patients were able to reduce or discontinue other ITP medications. Stimulation of platelet production by romiplostim may provide a new therapeutic option for patients with ITP.

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Introduction

Chronic immune thrombocytopenic purpura (ITP) is an autoimmune disorder that is characterised predominantly by antibody-mediated platelet destruction.[1–6] Available therapies—such as corticosteroids, intravenous immunoglobulins, splenectomy, rituximab, and cyclophosphamide—primarily focus on reduction of this platelet destruction.[7,8] However, recent evidence suggests that decreased platelet production might also have a role in ITP.[9,10] For example, kinetic studies have shown that platelet production is not increased (contrary to expectations) in over three-quarters of thrombocytopenic patients with chronic ITP,[11,12] and thrombopoietin concentrations are normal or near normal in patients with this disease.[13–17] Moreover, antiplatelet antibodies inhibit in-vitro growth of megakaryocyte precursor cells,[9,10] and bone marrow megakaryocytes in ITP can be apoptotic.[18] Often, therapies aimed at reduction of platelet destruction are either ineffective or poorly tolerated. Therefore, treatments aimed at increasing platelet production, alone or in combination with existing therapies, provide an opportunity to improve outcomes in patients with this chronic disease.

Romiplostim (formerly know as AMG531) is a novel thrombopoiesis stimulating protein (peptibody) that binds to and activates the human thrombopoietin receptor despite having no sequence homology with human thrombopoietin.[19,20] Romiplostim produces a

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dose-dependent increase in platelet counts in healthy volunteers[21] and improves platelet counts during short-term use in patients with chronic ITP.[19,22] In a small, randomised, placebo-controlled trial of weekly injections of romiplostim for 6 weeks (1 or 3 μg/kg) versus placebo, 12 of 16 ITP patients who were given romiplostim with baseline platelet counts of 30×10⁹/L or less (50×10⁹/L or less if on stable doses of corticosteroids) had their platelet counts at least doubled and increased to more than 50×10⁹/L; mean peak platelet counts were 135×10⁹/L and 241×10⁹/L for 1 μg/kg and 3 μg/kg romiplostim, respectively.[19] Romiplostim caused no major adverse events in these studies.[19,21,22]

We aimed to assess the efficacy, safety, and optimum dosing of romiplostim in the maintenance treatment of splenectomised and non-splenectomised patients with chronic ITP.

Methods

Study design and patients

We undertook two parallel prospective, multicentre, international phase III studies that were randomised, placebo-controlled, double-blind trials, lasting for 6 months. Study designs were identical except that one trial enrolled patients who had undergone splenectomy 4 weeks or more before entry, whereas the other enrolled patients who had not had a splenectomy.

Patients with ITP (according to American Society of Hematology guidelines)[4] were enrolled into both studies from 35 sites in the USA and Europe between March 1, 2005, and Dec 31, 2006. Institutional review boards at all centres approved the protocols and all patients provided written informed consent. Except for splenectomy status, eligibility criteria for both studies were identical and included mean platelet count less than 30×10⁹/L (with none >35×10⁹/L) during screening; age 18 years or older; no active malignancy or history of stem cell disorder; creatinine concentration 176·8 μmol/L or less, bilirubin no more than 1·5 times upper limit of normal, and haemoglobin 90 g/L or higher. Patients older than 60 years were required to have a bone-marrow examination consistent with the diagnosis of ITP. Patients could receive concurrent ITP therapy with corticosteroids, azathioprine, or danazol at a constant dose and schedule. We used the following intervals since the last administration of other ITP therapy: 2 weeks for intravenous immunoglobulin or anti-D immunoglobulin, 8 weeks for alkylating agents, 14 weeks for rituximab, and 4 weeks for all other treatments.

Procedures

Romiplostim (Amgen Inc, Thousand Oaks, CA, USA) and placebo were supplied in identical vials containing a lyophilised powder that was reconstituted with sterile water for subcutaneous injection. After reconstitution, both vials contained 10 mM histidine, 4% mannitol, 2% sucrose, and 0·004% polysorbate 20. Placebo vials did not contain the 0·5 mg/mL romiplostim protein that was present in romiplostim vials.

Patients were randomly assigned 2:1 to receive weekly subcutaneous injections of romiplostim or placebo for 24 weeks (stratified according to concurrent use of ITP treatment). The random allocation sequence was generated by Amgen Inc (Thousand Oaks, CA, USA) with the blocked randomisation method. Clinphone was used to randomly assign patients into the study with the interactive voice response system.

The starting dose of study drug (romiplostim or placebo) was 1 μg/kg. To achieve the target platelet count of 50×10⁹/L to 200×10⁹/L, doses could be increased according to the following algorithm: 2 μg/kg every week if the count was 10×10⁹/L or less and 2 μg/kg every 2 weeks if 11×10⁹/L to 50×10⁹/L. Once platelets reached more than 50×10⁹/L, the maintenance algorithm was used: dose was increased by 1 μg/kg every week if 10×10⁹/L or less; increased by 1 μg/kg after 2 weeks if 11×10⁹/L to 50×10⁹/L; reduced by 1 μg/kg after 2 consecutive weeks at 201×10⁹/L to 400×10⁹/L; withheld if more than 400×10⁹/L and subsequent doses reduced by 1 μg/kg and given after count was less than 200×10⁹/L. The maximum allowed dose was 15 μg/kg.

During the first 12 weeks only, reductions in concurrent ITP therapies were allowed when platelet counts were more than 100×10⁹/L. Increases in concurrent ITP therapies or the use of rescue drugs were allowed at any point in the study at the discretion of the investigator.

After 24 weeks, study treatment was discontinued and platelet counts monitored every week. Patients completed the study at week 36 or once platelet counts were less than 50×10⁹/L. All patients who completed the study were eligible to be screened for participation in an open-label extension study of romiplostim.

All outcome measures were prospectively defined before the start of the studies. A weekly platelet response was defined as a platelet count of 50×10⁹/L or more at a weekly study visit. Unless otherwise noted, platelet responses that occurred within 8 weeks after rescue drugs were used were not included in the efficacy analyses or in the determination of any other measures for platelet outcome. Rescue medication was defined as an increased dose of concurrent ITP therapy, or the use of any new drug to increase platelet counts. A durable platelet response (primary efficacy measure) was defined as weekly platelet responses during 6 or more weeks of the last 8 weeks of treatment. Patients who received rescue medication at any time during the study could not be counted as having a durable response. A transient platelet response was defined as four or more weekly platelet responses without a durable platelet response from week 2 to 25. Additional secondary endpoints were the frequency of overall platelet response (durable plus transient rates of platelet response), the number of weekly platelet responses, the proportion of patients needing rescue drugs, and the frequency of durable platelet

response with a stable dose (dose maintained within 1 μg/kg during the last 8 weeks of treatment). We also assessed changes in concurrent ITP therapies.

We analysed blood samples for thrombopoietin and antibodies against romiplostim.[19] Adverse events were rated on a scale of 1=mild, 2=moderate, 3=severe, 4=life threatening, and 5=fatal.

Statistical analysis

The sample size of 60 participants with a 2:1 randomisation ratio (40 in the romiplostim group and 20 in the placebo group) was chosen to provide adequate power to show that the efficacy of romiplostim, measured by the durable platelet response, was significantly better than placebo. The probability of achieving a durable platelet response with romiplostim and placebo was estimated at 50% and 10%, respectively. This sample size had about 87% power to detect the difference in the incidence of durable platelet response between romiplostim and placebo with a two-sided Fisher's exact test at a significance level of 0·05. Analysis was per protocol.

We summarised demographics, baseline characteristics, and haematological and other laboratory values with descriptive statistics. The incidences of durable and overall platelet responses, proportion of patients needing rescue drugs, and incidence of achieving stable dose were compared between the romiplostim and placebo groups by use of the Cochran-Mantel-Haenszel test stratified by baseline concurrent ITP therapy (yes/no).[23,24] Exact 95% CIs for the incidence were provided for each treatment group and normal approximated 95% CIs were given for the difference between treatment groups.[25] The common odds ratio was estimated together with the 95% CI. The number of weeks with platelet response for both treatment groups was summarised and compared by use of the analysis of variance model with treatment and baseline ITP therapy as predictors in the model.[26,27] To mitigate violation of the model assumptions, we used the Cochran-Mantel-Haenszel test with rank and stratified by baseline concurrent ITP therapy as a secondary analysis to ensure robustness.

These studies are registered with ClinicalTrials.gov, numbers NCT00102323 and NCT00102336

Role of the funding source

This study was funded by Amgen Inc, Thousand Oaks, CA, USA. In collaboration with the investigators, Amgen designed the study, did statistical analyses, and interpreted the data, which Amgen holds. Amgen collected the data and representatives (JLN and DMG) participated in the writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. All patients received at least one dose of investigational product. One non-splenectomised patient randomly assigned to placebo received three doses of romiplostim in error and was included in the safety analysis as a patient given romiplostim and in the efficacy analysis as a patient given placebo.

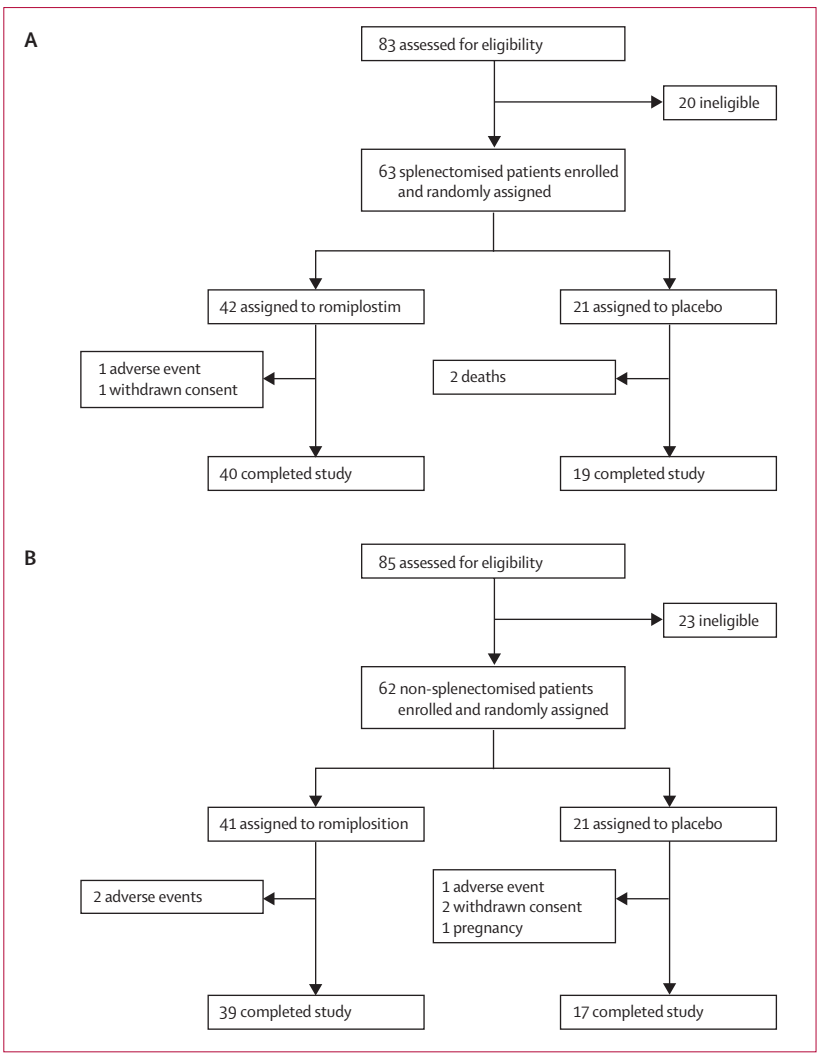

Figure 1: **Trial profile for splenectomised (A) and non-splenectomised patients (B)**

Table 1 shows baseline characteristics and patient demographics. All characteristics were comparable in the placebo and romiplostim treatment groups in both studies, but splenectomised patients had a longer duration of ITP, more previous ITP treatments, slightly lower baseline platelet counts, and higher baseline thrombopoietin concentrations than did non-splenectomised patients. The median time since splenectomy was 6·6 (range 0·2–43) years. The most common previous treatments in all patients were corticosteroids (118/125 [94%] patients; 62/63 splenectomised and 56/62 non-splenectomised patients) and intravenous immunoglobulins (100/125 [80%] of patients; 59/63 splenectomised and 41/62 non-splenectomised patients).

	Splenectomised patients		Non-splenectomised patients		All patients from both studies		
	Placebo (n=21)	Romiplostim (n=42)	Placebo (n=21)	Romiplostim (n=41)	All placebo (n=42)	All romiplostim (n=83)	Total (n=125)
Age (years)	56 (26–72)	51 (27–88)	46 (23–88)	52 (21–80)	52 (23–88)	52 (21–88)	52 (21–88)
Women	11 (52%)	27 (64%)	16 (76%)	27 (66%)	27 (64%)	54 (65%)	81 (65%)
Race							
White	19 (91%)	34 (81%)	18 (86%)	31 (76%)	37 (88%)	65 (78%)	102 (82%)
Black or African American	2 (10%)	3 (7%)	1 (5%)	3 (7%)	3 (7%)	6 (7%)	9 (7%)
Hispanic or Latino	0	3 (7%)	2 (10%)	3 (7%)	2 (5%)	6 (7%)	8 (6%)
Other*	0	2 (5%)	0	4 (10%)	0	6 (7%)	6 (5%)
Weight (kg)	89 (57–169)	77 (45–138)	71 (52–123)	78 (44–134)	81 (52–169)	78 (44–138)	79 (44–169)
Duration of ITP (years since diagnosis)	8·50 (1·1–31·4)	7·75 (0·6–44·8)	1·60 (0·1–16·2)	2·20 (0·1–31·6)	NA	NA	NA
≥3 previous treatments	20 (95%)	39 (93%)	5 (24%)	15 (37%)	26 (60%)	54 (65%)	79 (63%)
Platelet count (10^9/L)†	15 (2–28)	14 (3–29)	19 (5–31)	19 (2–29)	18 (2–31)	16 (2–29)	16 (2–31)
Thrombopoietin concentration (pg/mL)‡	124 (31–744)	113 (31–586)	81 (31–1848)	94 (31–1228)	108 (31–1848)	102 (31–1228)	103 (31–1848)
Receiving concurrent ITP therapy	6 (29%)	12 (29%)	10 (48%)	11 (27%)	16 (38%)	23 (28%)	39 (31%)

Data are median (minimum–maximum) or number (%). ITP=immune thrombocytopenic purpura. NA=not applicable. *Includes Asian and native Hawaiian or other Pacific Islander. †Baseline platelet count=mean of platelet counts at days –8, –2, and predose on day 1. ‡Normal thrombopoietin concentrations range from 32 to 246 pg/mL.

Table 1: **Patient demographics and baseline characteristics**

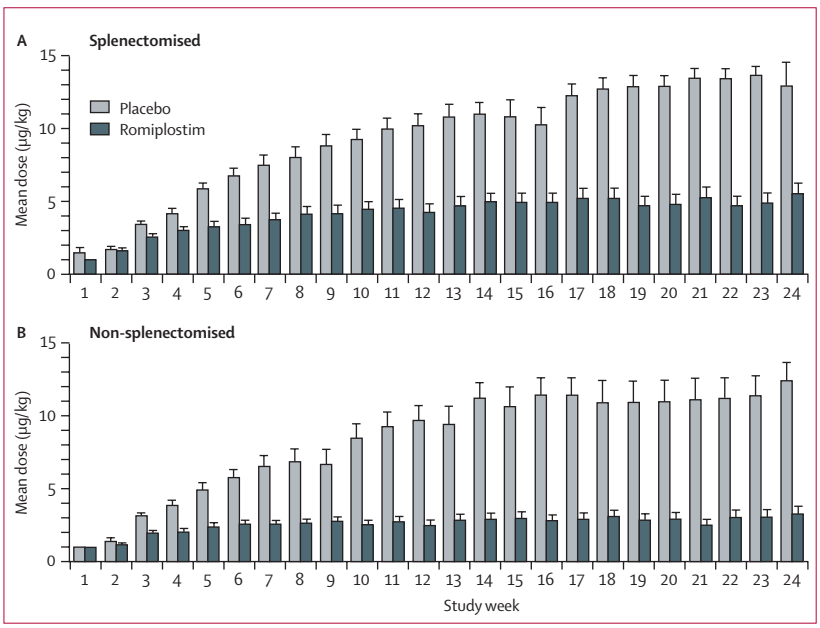

Figure 2: **Mean dose of romiplostim or placebo per week at every study visit for splenectomised (A) and non-splenectomised (B) patients**

Error bars show SEM. Throughout the 24-week study period, the median dose of romiplostim needed to maintain target platelet counts of 50×10^9/L to 200×10^9/L was roughly 3 µg/kg in splenectomised patients and 2 µg/kg in non-splenectomised patients.

Treatment dose was adjusted to achieve and maintain a target platelet count of 50×10^9/L to 200×10^9/L. There was a substantial difference in the dosing patterns between patients given placebo and those given romiplostim in both studies (figure 2). In those given placebo, the mean dose increased throughout the first 12 weeks to more than 10 µg/kg compared with 3–4 µg/kg for those given romiplostim. During the first 12 weeks, 95% (20/21) of splenectomised and 90% (19/21) of non-splenectomised patients given placebo had three or more dose increases. By contrast, 45% (19/42) of splenectomised and 24% (ten of 41) of non-splenectomised patients assigned to romiplostim had three or more dose increases during the same period. Patients who achieved a durable platelet response had a lower median dose of romiplostim during the last 8 weeks than did those who did not achieve this response (3 [range 0·0–7·0] µg/kg *vs* 5·3 [0·5–15·0] µg/kg in splenectomised patients; 1 [0·3–7·0] µg/kg *vs* 3 [1·0–15·0] µg/kg in non-splenectomised patients).

A target platelet count of 50x10^9/L or more (platelet response) was achieved by 25% of both splenectomised and non-splenectomised patients given romiplostim after 1 week and by 50% within 2–3 weeks. Between weeks 18 and 25 (during when the durable response was assessed), median weekly platelet counts for patients given romiplostim ranged from 56×10^9/L to 85×10^9/L for splenectomised patients and from 63×10^9/L to 96×10^9/L for non-splenectomised patients (figure 3). In the placebo groups, median weekly platelet counts during these weeks ranged from 13×10^9/L to 21×10^9/L for splenectomised patients and from 29×10^9/L to 38×10^9/L for non-splenectomised patients (figure 3). During weeks 7–25, the number of patients given romiplostim achieving a platelet response every week ranged from 19/39 (49%) to 29/41 (73%) for splenectomised patients and from 23/38 (61%) to 32/39 (82%) for non-splenectomised patients. Within 2 weeks of discontinuation of romiplostim, 37 of 51 (73%) patients who responded at the end of the study had platelet counts less than 50×10^9/L. Only seven of the 83 patients given romiplostim (two splenectomised

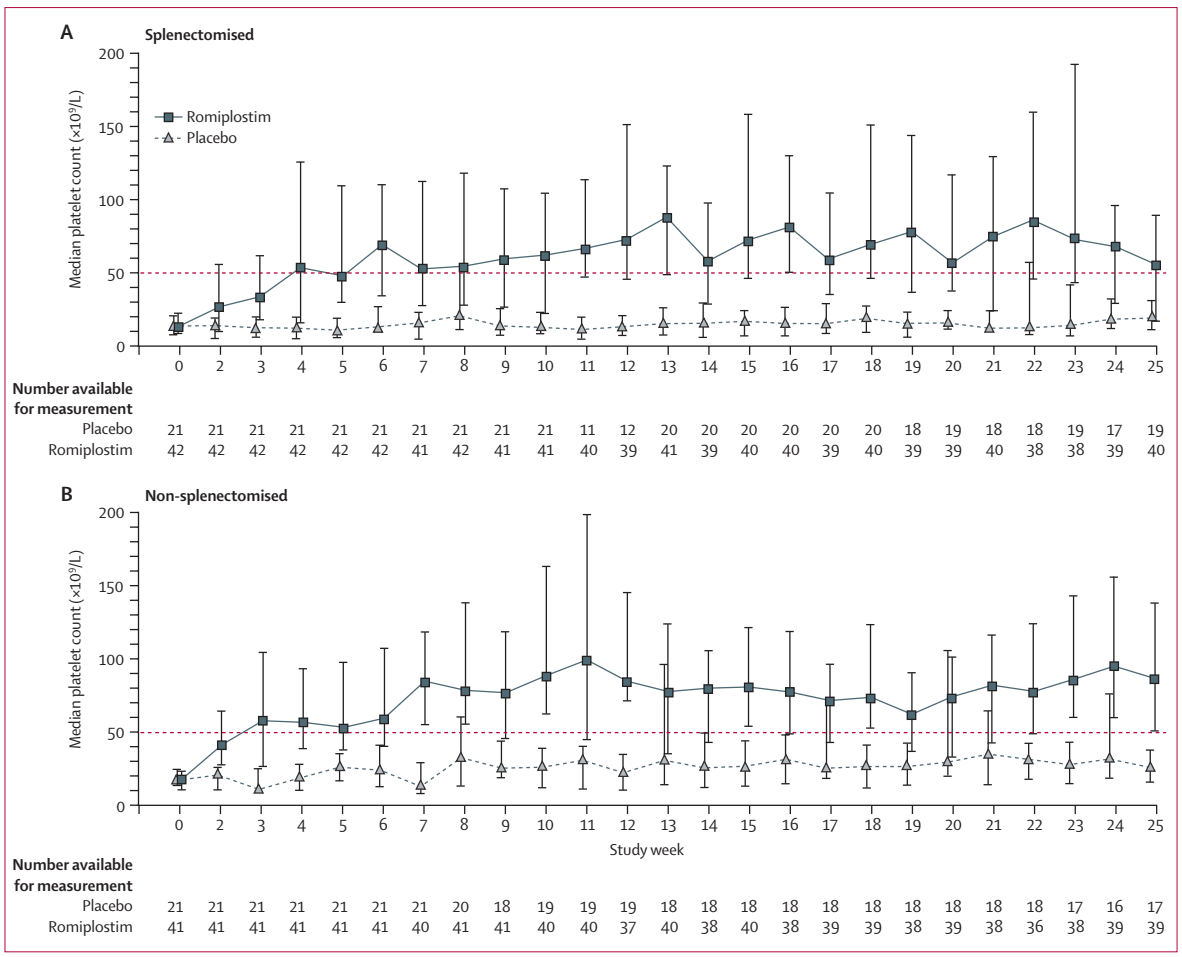

Figure 3: **Median platelet count at every weekly study visit for splenectomised (A) and non-splenectomised (B) patients**
Data includes all patients, even those who received rescue drugs. Error bars indicate the range from the first to third quartiles. Dashed line indicates platelet count of 50×10⁹/L.

and five non-splenectomised patients) maintained a platelet count of 50×10⁹/L or more 12 weeks after discontinuation of the drug.

The durable response rate—at least 6 weeks with platelet counts of 50×10⁹/L or more during the last 8 weeks of treatment—in patients given romiplostim was significantly greater than in those given placebo in both studies (difference in proportion of splenectomised patients responding 38% [95% CI 23·4–52·8], p=0·0013; difference in proportion of non-splenectomised patients responding 56% [38·7–73·7], p<0·0001; table 2). Moreover, 13 (31%) splenectomised and 21 (51%) non-splenectomised patients given romiplostim achieved a durable platelet response with a stable dose of the study drug (plus or minus 1 μg/kg during the last 8 weeks). Across both studies these patients needed a wide range of doses (1–7 μg/kg) to maintain this response.

Although not achieving a durable platelet response, 40% (17/42) of splenectomised patients and 27% (11/41) of non-splenectomised patients given romiplostim had a transient platelet response (≥4 weekly platelet responses from week 2 to 25). Therefore, the overall platelet response rate (either durable or transient platelet response) was 88% (36/41) in non-splenectomised and 79% (33/42) in splenectomised patients given romiplostim compared with 14% (three of 21) of non-splenectomised and no splenectomised patients given placebo (p<0·0001 figure 4). Both non-splenectomised and splenectomised patients given

	Splenectomised		Non-splenectomised		Total	
	Placebo (n=21)	Romiplostim (n=42)	Placebo (n=21)	Romiplostim (n=41)	Placebo (n=42)	Romiplostim (n=83)
Incidence rate as defined in the protocol*	0	16 (38%)	1 (5%)	25 (61%)	1 (2%)	41 (49%)
Incidence rate disregarding whether rescue drugs were received	1 (5%)	19 (45%)	3 (14%)	27 (66%)	4 (10%)	46 (55%)

Data are number (%). *Protocol specifically stated that any patient who received any rescue medication at any time during the study could not be counted as having a durable response.

Table 2: **Incidence of durable platelet response**

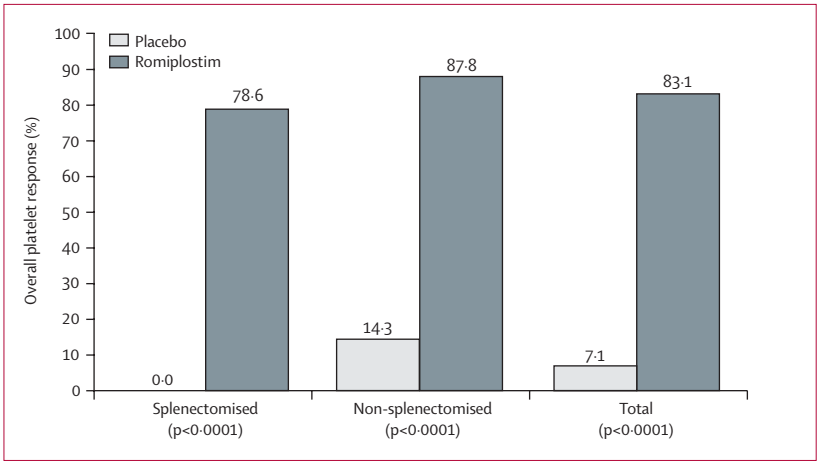

Figure 4: **Patients with overall platelet response**
Overall platelet response defined as durable platelet response or four or more weekly platelet responses at any time during the study.

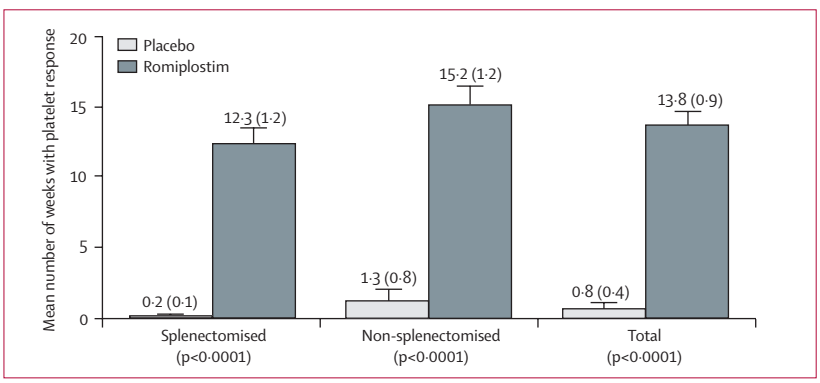

Figure 5: **Number of weeks with platelet response during the 24-week study**
Numbers in parentheses show SEM.

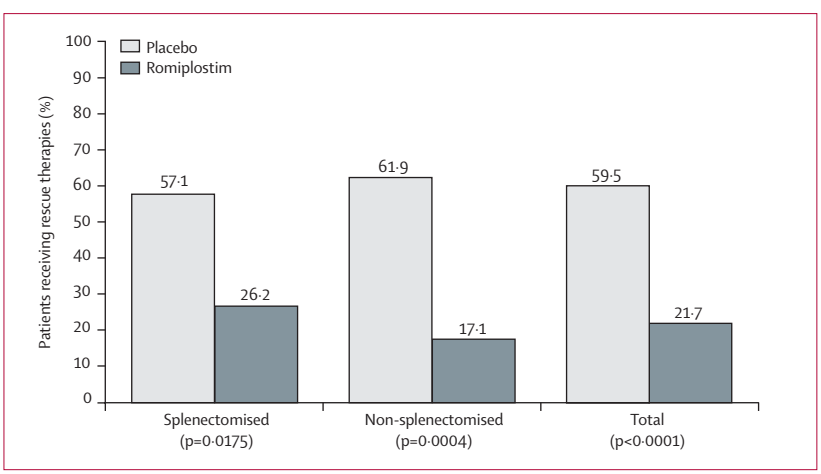

Figure 6: **Patients receiving rescue therapies**

romiplostim had a platelet count of 50×10⁹/L or higher on more of the 24 total study visits than did those given placebo (figure 5).

Across both studies, 23 (12 splenectomised, 11 non-splenectomised) patients with romiplostim and 16 (six splenectomised and ten non-splenectomised) with placebo received concurrent ITP therapy with corticosteroids, azathioprine, and/or danazol. During the first 12 weeks of the study (as allowed by the protocol) 12 of 23 (52%) patients given romiplostim (eight of 12 splenectomised and four of 11 non-splenectomised patients) and three of 16 (19%) given placebo (none of six splenectomised and three of ten non-splenectomised patients) discontinued all of their concurrent ITP drugs. An additional eight of 23 (35%) given romiplostim (four of 12 splenectomised and four of 11 non-splenectomised patients) and three of 16 (19%) given placebo (one of six splenectomised and two of ten non-splenectomised patients) reduced at least one of their concurrent ITP drugs by more than 25%. Moreover, more patients in the placebo group than in the romiplostim group received rescue drugs to increase platelet counts to prevent or treat bleeding ($p<0·0001$, figure 6).

A multivariate analysis showed that baseline weight less than 70 kg ($p=0·0106$) and no splenectomy ($p=0·0306$) were the only clinical or laboratory variables significantly associated with increased rates of durable response. Lower weight was also significantly associated with a greater number of weeks with a platelet response ($p=0·008$) and lower use of rescue drugs ($p=0·0285$). We recorded no relation between the achievement of a durable response and either baseline thrombopoietin concentrations or previous or concurrent use of other ITP therapies.

Analysis of the individual studies indicated no difference in safety profile between splenectomised and non-splenectomised ITP patients assigned to romiplostim, and therefore we pooled safety data for all patients in placebo and romiplostim groups. Adverse events were reported in 39 of 41 (95%) patients receiving placebo and in all 83 (100%) patients receiving romiplostim. Almost all adverse events were rated as mild to moderate. Table 3 shows the adverse events with an incidence of 10% or more. Significant bleeding events (those rated as severe, life threatening, or fatal) were reported in five of 41 (12%) patients in the placebo group and in six of 84 (7%) patients in the romiplostim group, invariably at platelet counts less than 20×10⁹/L.

Two patients in the placebo group died during the study; one from cerebral haemorrhage and one from pulmonary embolism. Another patient in the placebo group died from atypical pneumonia (after an intracranial haemorrhage because of trauma) 5 weeks after study completion. One patient assigned to romiplostim died from intracranial haemorrhage (after starting aspirin to treat thrombosis and then discontinuing romiplostim) 1 day after study completion.

There were two serious adverse events that were assessed as treatment-related. One splenectomised, non-responding patient assigned to romiplostim, who had increased baseline bone marrow reticulin, developed additional reticulin after 7 weeks of treatment but returned to baseline

	Placebo (n=41)	Romiplostim (n=84)
Headache	13 (32%)	29 (35%)
Fatigue	12 (29%)	28 (33%)
Epistaxis	10 (24%)	27 (32%)
Arthralgia	8 (20%)	22 (26%)
Contusion	10 (24%)	21 (25%)
Petechiae	9 (22%)	14 (17%)
Diarrhoea	6 (15%)	14 (17%)
Upper respiratory tract infection	5 (12%)	14 (17%)
Dizziness	0	14 (17%)
Insomnia	3 (7%)	13 (16%)
Myalgia	1 (2%)	12 (14%)
Back pain	4 (10%)	11 (13%)
Nausea	4 (10%)	11 (13%)
Pain in extremity	2 (5%)	11 (13%)
Cough	7 (17%)	10 (12%)
Anxiety	5 (12%)	9 (11%)
Gingival bleeding	5 (12%)	9 (11%)
Abdominal pain	0	9 (11%)
Nasopharyngitis	7 (17%)	7 (8%)
Ecchymosis	6 (15%)	6 (7%)

*Because no statistically significant difference between splenectomised and non-splenectomised patients was recorded, the results for this analysis were pooled.

Table 3: **Adverse events occurring in at least 10% of patients in either treatment group***

when the next biopsy sample was taken 14 weeks after termination of romiplostim. An 82-year-old patient receiving romiplostim who had extensive peripheral vascular disease and atrial fibrillation and who had a radial artery thromboembolectomy 8 months previously had a right popliteal artery thrombosis at a platelet count of 11×10^9/L. He was successfully treated with embolectomy and anticoagulation and continued the study.

Thrombosis occurred in one patient assigned to placebo and two assigned to romiplostim. As described above, one patient taking placebo died of pulmonary embolism and one patient taking romiplostim developed a popliteal artery thrombosis. A patient taking romiplostim with cerebrovascular disease, congestive heart failure, diabetes, and hypertension had a cerebrovascular accident at week 21 at a platelet count of 107×10^9/L; this adverse event was assessed as unrelated to administration of romiplostim.

No patient tested positive for antibodies against romiplostim or thrombopoietin. Apart from platelet counts, we recorded no clinically significant treatment-related changes in vital signs, or in haematological or serum chemistry values.

Discussion

In these two randomised, controlled trials, romiplostim was a well-tolerated and effective treatment for patients with ITP. Platelet increases were seen within 1–2 weeks and were sustained throughout 24 weeks of treatment in both splenectomised and non-splenectomised patients. The target platelet count was achieved within 2–3 weeks by over half of patients given romiplostim, with more than four-fifths achieving an overall platelet response and about half achieving a durable response (two-fifths while taking a stable dose of romiplostim). Our placebo-controlled study has shown the efficacy of romiplostim for ITP patients who did not respond to splenectomy.[28]

The rigorous primary outcome measure, a durable platelet response, was chosen to assess the efficacy of romiplostim in maintaining a stable and adequate platelet count during the last 8 weeks of the study, once dosing had been optimised and concurrent ITP drugs had been reduced or withdrawn. The overall platelet response was less strictly defined, requiring either a durable response or at least four of the weekly platelet counts greater than 50×10^9/L at any time during the 24-week study period. The greater than 80% overall response rate for romiplostim was as high as that reported for corticosteroids and intravenous immunoglobulins, and higher than that reported for other treatments such as anti-D, azathioprine, danazol, and splenectomy.[4,29–33] This finding is especially striking because the patients in these two studies were a very refractory group, including 63 who did not respond to splenectomy and several other treatments, and was also shown by the three deaths in the placebo group. The high rate of efficacy in this study, greater than that previously reported for romiplostim,[19,22] was almost certainly a result of the ability to make individualised dosing adjustments to achieve the target platelet range.

Two other important findings in patients given romiplostim were a lower rate of use of rescue drugs and the ability to discontinue or reduce the use of concurrent ITP drugs such as corticosteroids. More patients might have further reduced or discontinued their corticosteroid doses but the protocol did not allow such reductions after the first 12 weeks of the study.

Despite high overall response rates, not all patients achieved a durable response. This finding might show limitations in the study protocol or variations in the biological severity of ITP within the patient population. In some patients, a lack of durable response could have been because of the reduction of concurrent ITP therapies, leading to decreases in platelet counts and an increased likelihood of use of rescue drugs; according to the study guidelines, use of any rescue drugs, irrespective of effect, required that the patient be excluded from the primary endpoint analysis and that all platelet counts for the next 8 weeks be excluded from the analysis of other endpoints of platelet response. In other patients, the fairly narrow target platelet count range (50×10^9/L to 200×10^9/L) was exceeded, leading to frequent dose changes and subsequent cycling of the platelet count. Some patients with chronic ITP might have an innate cycling of their platelet count[34] that could affect their response to treatment. Furthermore, individual variations in the relative effect of antiplatelet antibodies on platelet destruction and production might explain differences in durable response rates. Finally,

although all patients fulfilled the American Society of Hematology criteria for ITP,[4] a few might have had an inherited defect in platelet production that mimicked ITP.

In patients achieving durable platelet responses at a stable dose, a seven-fold range of romiplostim doses was needed to maintain the target platelet count range. This wide difference in dose is presumably related to poorly understood individual variations in disease severity or pharmacodynamics, which could be affected by patient weight.

Although limited by the fairly few patients, multivariate analyses identified weight less than 70 kg and the absence of splenectomy to be associated with a high durable response rate. The effect of weight remains unexplained, but it could be related to pharmacokinetic differences. The effect of splenectomy on romiplostim response is not surprising. Splenectomised patients had more severe ITP as shown by a higher number of previous therapies, higher rates of use of concurrent ITP therapy at baseline, and a tendency to need higher romiplostim doses for an initial response. They also seemed to have more variability in response to romiplostim than did non-splenectomised patients. Nonetheless, an overall platelet response was seen in nearly four-fifths of splenectomised patients and many had counts exceeding 200×10^9/L, suggesting that most splenectomised patients could also be effectively managed with romiplostim.

Romiplostim was well tolerated, and most adverse events were mild and related to the underlying thrombocytopaenia. The clinical significance of the apparent increase in dizziness, insomnia, myalgia, extremity pain, and abdominal pain in patients given romiplostim cannot be fully assessed because of the fairly small study population. Larger, continuing studies are being done to assess this question further.[35] However, no patient discontinued romiplostim because of these complaints.

Two uncommon, severe adverse effects were reported with romiplostim: bone marrow reticulin formation and thromboembolism. One non-responding patient developed increasing bone marrow reticulin that improved with discontinuation of the drug without any evidence of a clonal myeloproliferative disorder. No placebo-treated patients developed increased reticulin. Similar reversible increases in bone marrow reticulin have been noted in animals and human beings exposed to romiplostim[20,36] and they are thought to be caused by increased bone-marrow transforming growth factor β released from megakaryocytes and platelets.[37,38]

Two arterial thromboembolic events were reported in elderly patients with previous histories of vascular disease who were given romiplostim and who had platelet counts above their baseline but below the normal range. Whether these events were due to administration of romiplostim or to the increased platelet count is unknown. It should be noted that romiplostim does not directly increase platelet activation.[20,21] However, measurements in arterial vascular shunts in baboons have clearly shown a linear increase in platelet deposition with an increase in platelet counts after treatment with recombinant thrombopoietin.[39] Thromboembolic events also occurred in one patient who received placebo.

Contributors

DJK, JBB, VP, TBG, DMG, and JLN were responsible for writing this article. DJK, JBB, RML, VP, TBG, FMS, LMA, JNG, CMK, MAS, HAL, FTS, JTMdeW, EB, THG, ACN, JSW, SIH, CG, FL, AEL, MDT, HRT, J-FV, FJC, RSG, DHH, RLR, LR, MRS, DMG, and JLN made substantial contributions to study conception and design, analysis and interpretation of data, and critically reviewed and approved the final version of the report. DJK, JBB, RML, VP, TBG, FMS, LMA, JNG, CMK, MAS, HAL, FTS, JTMdeW, EB, THG, ACN, JSW, SIH, CG, FL, AEL, MDT, HRT, J-FV, FJC, RSG,DHH, RLR, LR, and MRS enrolled patients and collected data.

Conflict of interest statement

DJK receives research support from Amgen and GSK. JBB receives research support from Amgen, Biogen-IDEC, Cangene, Genentech, GSK, and Sysmex. He participates for Baxter in their speaker's bureau programme. He owns stock in Amgen and GSK. He participates in Advisory Boards for Amgen, GSK, and Baxter. RML, JNG, and TBG have received consultant fees and research support from Amgen. LMA has received a research grant from Amgen. CMK has received consultancy fees and research fees from Amgen, AKARX, and GSK. HAL has received research support from Amgen. AN has received consultancy fees from Amgen and GSK and research support from GSK. JSW has received research support from Amgen. AEL has received research support from Amgen and has participated in an advisory board meeting for Amgen. DHH has received a research grant from and participated in a speaker's bureau for Amgen. LR has been on an Amgen advisory board that focused on erythropoietic hormones 2 years ago. DMG and JLN are employees of Amgen. VP, MS, FTS, JTMdeW, EB, THG, SIH, CG, FL, MDT, HRT, J-FV, FJC, RSG, RLR, MRS, and FMS declare that they have no conflict of interest.

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