





Efficacy and safety of romiplostim in refractory aplastic anaemia: a Phase II/III, multicentre, open-label study

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Abstract

A previous dose-finding study has suggested that romiplostim is effective in patients with refractory aplastic anaemia (AA) and 10 µg/kg once weekly was recommended as a starting dose. In this Phase II/III, multicentre, open-label study, romiplostim was administered subcutaneously at a fixed dose of 10 µg/kg once weekly for 4 weeks (weeks 1–4) followed by weekly doses (5, 10, 15 and 20 µg/kg) titrated by platelet response for up to 52 weeks (weeks 5–52). A total of 31 patients with AA who were refractory to immunosuppressive therapy (IST) and thrombocytopenia (platelet count of $\leq 30 \times 10^9/l$) were enrolled. The primary efficacy endpoint of the proportion of patients achieving any haematological (platelet, neutrophil and erythrocyte) response at week 27 was 84% [95% confidence interval (CI) 66–95%]. Trilineage response was 39% (95% CI 22–58%) at week 53. The most common treatment-related adverse events (AEs) were headache and muscle spasms (each 13%). All AEs were mild or moderate except for three patients with Grade 3 hepatic AEs; no AEs necessitated romiplostim discontinuation. Two patients developed cytogenetic abnormalities, of whom one returned to normal karyotype at last follow-up. High-dose romiplostim is effective and well tolerated in the treatment of patients with AA refractory to IST.

Keywords: aplastic anaemia, bone marrow failure, haematopoiesis, thrombopoietin.

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Introduction

Aplastic anaemia (AA) is a haematopoietic stem cell disorder characterised by pancytopenia and hypocellular bone marrow (BM). The proposed pathogenesis of AA is cytotoxic T-lymphocyte-mediated diminution of haematopoietic stem cells. Combination of anti-thymocyte globulin (ATG) and cyclosporin is the standard immunosuppressive therapy (IST) for patients with severe AA who are not candidates for haematopoietic stem cell transplantation (HSCT). Typical response rates to the first cycle of IST are about 60–70%, of which 30–60% eventually relapse.^{1–4} Other pharmacological treatments for IST-refractory AA or adjunctive therapies to IST have proven ineffective until reports with the thrombopoietin (TPO)-receptor agonist, eltrombopag.^{5–7}

Romiplostim is a Fc-peptide fusion protein (peptibody) that signals and activates intracellular transcriptional pathways via the TPO receptor.^{8,9} The possible mechanism of haematopoietic recovery by romiplostim or eltrombopag is stimulation of haematopoietic stem and progenitor cells (HSPCs), as the TPO receptor is expressed on HSPCs.^{10,11} A novel mechanism has been recently presented, which showed that eltrombopag can evade the inhibitory effect of interferon- γ on HSPCs and signal downstream of the TPO receptor to provide a stimulatory effect, whereas endogenous TPO is inhibited by interferon- γ by forming a heterodimer.¹²

Based on our previous findings of HSPCs stimulated by romiplostim, we suggest that the depleted HSPCs in severe AA can be expanded and maintained in responders to romiplostim for at least 1 year.⁷ Further, it was suggested that persistent stimulation of HSPCs requires high doses of romiplostim. In our dose-finding study,⁷ a platelet response at

week 9 was achieved in seven of 10 patients in the 10 $\mu\text{g}/\text{kg}$ cohort, three of nine patients in the 6 $\mu\text{g}/\text{kg}$ cohort and no patients in either the 3 $\mu\text{g}/\text{kg}$ or 1 $\mu\text{g}/\text{kg}$ cohort.

We therefore decided to use romiplostim 10 $\mu\text{g}/\text{kg}$ as a starting dose in the present open-label study, the aim of which was to determine the response rate, development of cytogenetic abnormalities and safety of romiplostim in patients with refractory AA.

Methods

Patients

Eligible patients included adults (aged ≥ 20 and ≥ 19 years in Japan and Korea respectively) with AA and thrombocytopenia (platelet count of $\leq 30 \times 10^9/\text{l}$) who were refractory to IST (ATG plus cyclosporin or cyclosporin monotherapy). Patients who were ineligible for ATG treatment due to older age or comorbidity and refractory to treatment with cyclosporin for at least 6 months were allowed to enrol in this study. Eastern Cooperative Oncology Group Performance Status score had to be 0–2 with preserved renal, hepatic and cardiovascular function. Exclusion criteria are provided in Data S1.

Study design

The study was approved by the Institutional Review Board at each study centre. All patients provided written informed consent prior to screening. The study was conducted in accordance with national laws and regulations, the International Conference on Harmonisation of Good Clinical

Practice guidelines, and the ethical principles of the Declaration of Helsinki. It was registered at clinicaltrials.gov (NCT02773290).

Eligible patients were recruited into this Phase II/III, multicentre, open-label study of romiplostim administered subcutaneously at a fixed dose of 10 µg/kg once weekly for 4 weeks (weeks 1–4) followed by titrated dose steps of 5, 10, 15 and 20 µg/kg once weekly up to 52 weeks (weeks 5–52). End of treatment assessment of efficacy was undertaken at week 53. All patients stopped treatment between weeks 53–56 and could continue romiplostim treatment from week 56 onwards into the extension phase of the clinical trial at the dose taken at week 53 regardless of response at that time. The concurrent administration of other treatments for AA (e.g. immunosuppressive agents, cyclosporin and anabolic hormones) was not permitted during the trial.

Romiplostim dose was adjusted depending on platelet response (see Table I for definitions of platelet, erythrocyte, neutrophil and trilineage response) and toxicity. Dose was increased by one step every 4 weeks until a platelet response was achieved. If the platelet count was $>200 \times 10^9/l$, the dose was reduced by one step. An outline of treatment interruption or dose reduction due to excessive platelet increase is shown in Figure S1.

The romiplostim dose was tapered with the intent to discontinue when trilineage haematopoiesis was achieved (for details see Data S1 and Table S1). Trilineage haematopoiesis was defined as platelet count of $>50 \times 10^9/l$, haemoglobin

concentration of >100 g/l and neutrophil count of $>1 \times 10^9/l$ maintained for 8 weeks with the same romiplostim dose without transfusion.

Efficacy

The primary endpoint was the proportion of patients achieving any haematological response (platelet, erythrocyte or neutrophil) at week 27 (see Table I for response definition). Secondary endpoints included: the proportion of patients with any haematological response at week 53; time from the first romiplostim administration to haematological response; proportion of patients with platelet transfusion independence or decreased transfusion requirement; and proportions of patients achieving platelet, erythrocyte or neutrophil response at weeks 27 and 53. Efficacy was analysed using the full analysis set. Transfusion independence was defined as a patient not having a platelet or red blood cell transfusion for ≥ 8 consecutive weeks. Statistical analysis is provided in Data S1.

Safety

Adverse events (AEs) were graded by National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. BM examination was undertaken before study enrolment, and at 6 and 12 months after romiplostim treatment with G-banding cytogenetic analysis. In addition, fluorescence *in situ* hybridisation (FISH) techniques were used for the detection of abnormalities of chromosome 7. Anti-romiplostim and anti-TPO antibodies including neutralising antibodies were monitored using cell-based assays (Biacore).

Pharmacokinetics

Blood samples were taken at regular intervals after dosing at weeks 1 and 4 in 13 patients for the determination of pharmacokinetic parameters. In the remaining patients, blood samples were taken immediately before dosing at intervals during treatment for the determination of trough romiplostim concentrations. Serum romiplostim concentrations were measured using a validated enzyme-linked immunosorbent assay with a lower limit of quantification of 0.015 µg/l. Pharmacokinetic parameters were determined using Phoenix WinNonlin 7.0.

Results

Patient characteristics

A total of 31 patients (24 in Japan and seven in Korea) were enrolled from June 2016 to May 2017 with data cut-off on September 2018 for analysis of patients completing 1 year of treatment. Patient demographic and clinical characteristics are summarised in Table II. The median (range) age was 46 (20–78) years. Severity of AA at baseline was transfusion-

Table I. Definition of platelet, erythrocyte, neutrophil and trilineage responses.

Platelet response
<ul style="list-style-type: none"> Platelets showed an increase of $\geq 20 \times 10^9/l$ above baseline; or Platelets showed an increase to $\geq 10 \times 10^9/l$ and by $\geq 100\%$ from baseline. No platelet transfusion for 8 weeks in patients who had received platelet transfusions in the 8 weeks prior to the first romiplostim dose.
Erythrocyte response
<ul style="list-style-type: none"> Increase in haemoglobin ≥ 90 g/l without red blood cell transfusion in patients with pre-treatment haemoglobin <90 g/l; or Cumulative red blood cell transfusion volume reduction of ≥ 4 units (1 unit = 200 ml) for 8 weeks in those who had received transfusion in the 8 weeks prior to the first romiplostim dose.
Neutrophil response
<ul style="list-style-type: none"> Neutrophils increased by $\geq 100\%$ in patients with baseline neutrophils $<0.5 \times 10^9/l$; or Neutrophils increased by $\geq 0.5 \times 10^9/l$ over baseline in patients with baseline neutrophils of 0.5 to $1 \times 10^9/l$.
Trilineage response
<ul style="list-style-type: none"> Patients achieving concurrent platelet, erythrocyte and neutrophil responses.

dependent non-severe (58%, $n = 18$), severe (29%, $n = 9$) or very severe (13%, $n = 4$).

Four patients discontinued (all with no haematological response) during treatment at weeks 16, 16, 24 and 31 respectively. After week 12, the maximum dose of romiplostim reached was 10 ($n = 4$), 15 ($n = 6$) and 20 $\mu\text{g}/\text{kg}$ once weekly ($n = 21$). The median (range) dose was 15.9 (3.1–18.8) $\mu\text{g}/\text{kg}/\text{week}$ over the study for the 27 patients who completed at week 53. The doses given to the patients at each week are detailed in Fig 1.

Efficacy

Haematological responses at weeks 27 and 53 are summarised in Table III and Fig 2 for the full analysis set. The

Table II. Baseline demographic and clinical characteristics ($N = 31$).

Characteristic	Value
Age, years, median (range)	46 (20–78)
Female/male, n (%)	22/9 (71/29)
Asian ethnicity, n (%)	31 (100)
BMI, kg/m^2 , median (range)	22 (18–35)
Time since diagnosis, years, median (range)	4.5 (0.1–16.8)
Aplastic anaemia severity, n (%)	
Non-severe	18 (58)
Severe	9 (29)
Very severe	4 (13)
ECOG PS score 0/1, n (%)	20/11 (65/35)
Prior treatment, n (%)	
ATG + cyclosporin*	22 (71)
Cyclosporin monotherapy	8 (26)
G-CSF	4 (13)
Other†	26 (84)
Time from last ATG dose, months, median (range)	42.4 (6.8–170.1)
Transfusion required in the 8-week period prior to romiplostim treatment, n (%)	
Platelets	15 (48)
RBCs	20 (65)
Both platelets and RBCs	12 (39)
Platelet count, $\times 10^9/\text{l}$, median (range)	14.0 (4–28)
Haemoglobin concentration, $\text{g}/\text{l}^\ddagger$, median (range)	71 (46–128)
Neutrophil count, $\times 10^9/\text{l}$, median (range)	0.867 (0.202–2.133)
Absolute reticulocyte count, $\times 10^9/\text{l}$, median (range)	50.2 (2.7–114.7)

ATG, anti-thymocyte globulin; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; G-CSF, granulocyte colony-stimulating factor; RBC, red blood cell.

*One patient for whom the date of ATG + cyclosporin administration was unclear and, per protocol, was excluded from analysis.

†Includes methenolone acetate ($n = 11$), prednisolone ($n = 10$), danazol ($n = 7$), methylprednisolone sodium succinate ($n = 6$), oxy-metholone ($n = 5$), methylprednisolone ($n = 2$), metenolone ($n = 1$), methylprednisolone acetate ($n = 1$) and stanozolol ($n = 1$).

‡ $n = 22$.

proportion of patients achieving any haematological response at week 27, the primary efficacy endpoint, was 84% [95% confidence interval (CI) 66–95%]. At week 27, platelet response was 65% (95% CI 45–81%), erythrocyte response 74% (95% CI 55–88%), neutrophil response 39% (95% CI 22–58%) and trilineage response 26% (95% CI 12–45%). Similar individual lineage responses were seen at week 53, although more patients achieved a trilineage response: platelet response 65% (95% CI 45–81%), erythrocyte response 68% (95% CI 49–83%), neutrophil response 48% (95% CI 30–67%) and trilineage response 39% (95% CI 22–58%). The proportion of patients achieving any haematological response at week 53 was 81% (95% CI 62–93%). The median (95% CI) time from the first administration to any haematological response was 37 (36–44) days at week 53 (Figure S2). The median (95% CI) time from first administration to trilineage response was 238 (105–not reached) days (Figure S3). Of the 15 patients who were platelet transfusion dependent at baseline, nine (60%) became transfusion independent at week 27 and 11 (73%) at week 53. *Post hoc* analyses of any haematological response rate at week 27 were conducted for various subgroups. There was no significant difference ($P = 0.133$) in response between patients subgroups with non-severe AA (94%, 95% CI 73–100%; $n = 18$) and those with severe/very severe AA (69%, 95% CI 39–91%; $n = 13$). Similarly, there was no significant difference ($P = 0.286$) in response between patient subgroups who had previously received ATG plus cyclosporin (77%, 95% CI 55–92%; $n = 22$) and those who had received cyclosporin monotherapy (100%, 95% CI 63–100%; $n = 8$).

Changes from baseline in mean platelet counts, neutrophil counts and haemoglobin concentration are shown in Fig 3. Values increased from baseline until weeks 10–18 and, thereafter, remained relatively constant or increased marginally through to week 53. Mean (\pm SD) platelet count at baseline was $13.9 (5.9) \times 10^9/\text{l}$ and increased to a maximum of $53.1 (42.2) \times 10^9/\text{l}$ (307% increase) at week 48. The mean (SD) haemoglobin concentration was $75.4 (19.2) \text{g}/\text{l}$ at baseline and increased to a maximum of $115.6 (22) \text{g}/\text{l}$ (66% increase) at week 49. The mean (SD) neutrophil count was $0.954 (0.511) \times 10^9/\text{l}$ at baseline and increased to a maximum value of $1.993 (1.184) \times 10^9/\text{l}$ (155% increase) at week 49. The mean (SD, range) duration of haematological response defined as the maximum duration of haematological response for each patient by week 53 was 251.1 (111.2, 14–344) days (Figure S4).

Six patients achieved trilineage haematopoiesis and absence of platelet transfusion for 4 weeks while receiving the lowest romiplostim dose of 5 $\mu\text{g}/\text{kg}/\text{week}$. Romiplostim discontinuation was firstly attempted in these six patients at weeks 11, 26, 28, 50, 51 and 51 respectively. The latter three patients maintained romiplostim discontinuation at data cut-off (week 56). Re-introduction of romiplostim at 5 $\mu\text{g}/\text{kg}/\text{week}$ was required in the former three patients because of loss of response after 5–9 weeks off romiplostim; these three

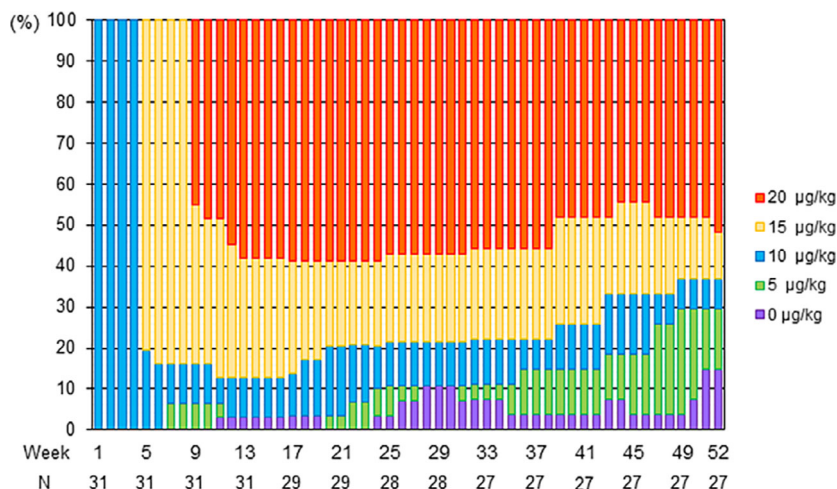


Fig 1. Romiplostim doses given to the patients each week.

patients achieved trilineage haematopoiesis again after re-introduction of romiplostim. BM cellularity data are provided in Table S2: of the 25 patients who achieved any haematological response at week 53, 11 (44%) and 16 (64%) showed increased cellularity at weeks 27 and 53 respectively.

Safety

The AEs occurring during romiplostim treatment are summarised in Table IV. The most common AEs were nasopharyngitis (42%), upper respiratory tract infection (26%), pyrexia (19%), headache (16%), diarrhoea (13%) and muscle spasms (13%). The most common treatment-related AEs were headache and muscle spasms (each 13%). There were no deaths and two patients had a serious AE (cervical pyogenic spondylitis and sepsis respectively), both of which were considered unrelated to romiplostim. No patients discontinued romiplostim because of AEs. AE severity was Grade 1/2 except for six patients who experienced Grade 3, three of which were drug-related [abnormal hepatic function,

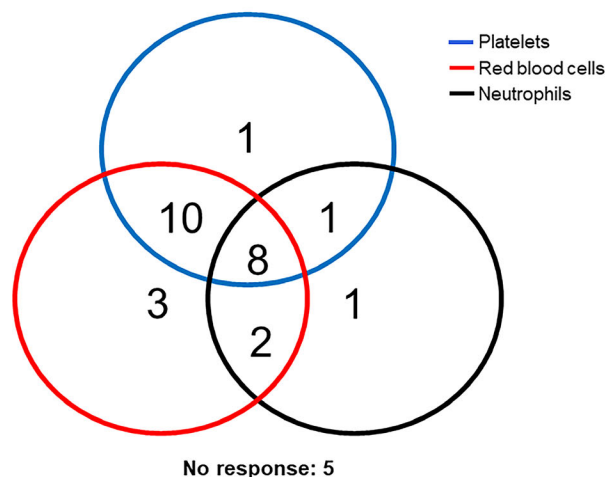
Table III. Haematological responses with romiplostim at weeks 27 and 53 (N = 31).

Haematological endpoint	No. of responders (%) [95% CI]	
	Week 27	Week 53
Any haematological response	26 (84) [66–95]	25 (81) [63–93]
Platelet response	20 (65) [45–81]	20 (65) [45–81]
Erythrocyte response	23 (74) [55–88]	21 (68) [49–83]
Neutrophil response	12 (39) [22–58]	15 (48) [30–67]
Trilineage response	8 (26) [12–45]	12 (39) [22–58]
Transfusion independent for both platelets and RBCs*	10 (83) [52–98]	9 (75) [43–95]

CI, confidence interval; RBC, red blood cell.

*These data indicate the number of responders among those who were dependent on both platelet and RBC transfusion at baseline (N = 12).

(A) Week 27



(B) Week 53

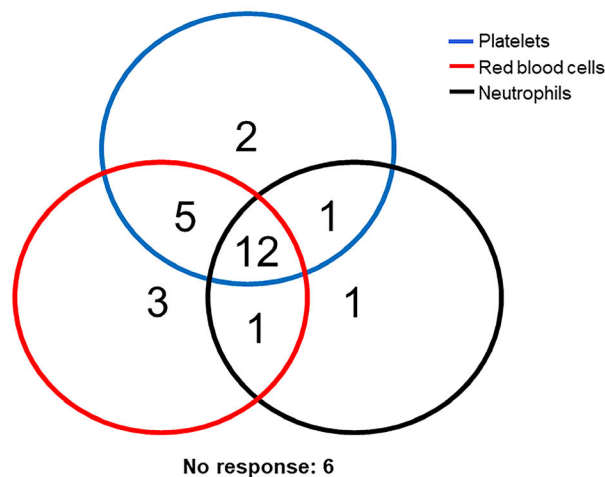


Fig 2. Haematological responses to romiplostim at weeks 27 and 53. Venn diagrams show the numbers of patients with single, bilineage and trilineage responses at (A) week 27 and (B) week 53 for the full analysis set (N = 31).

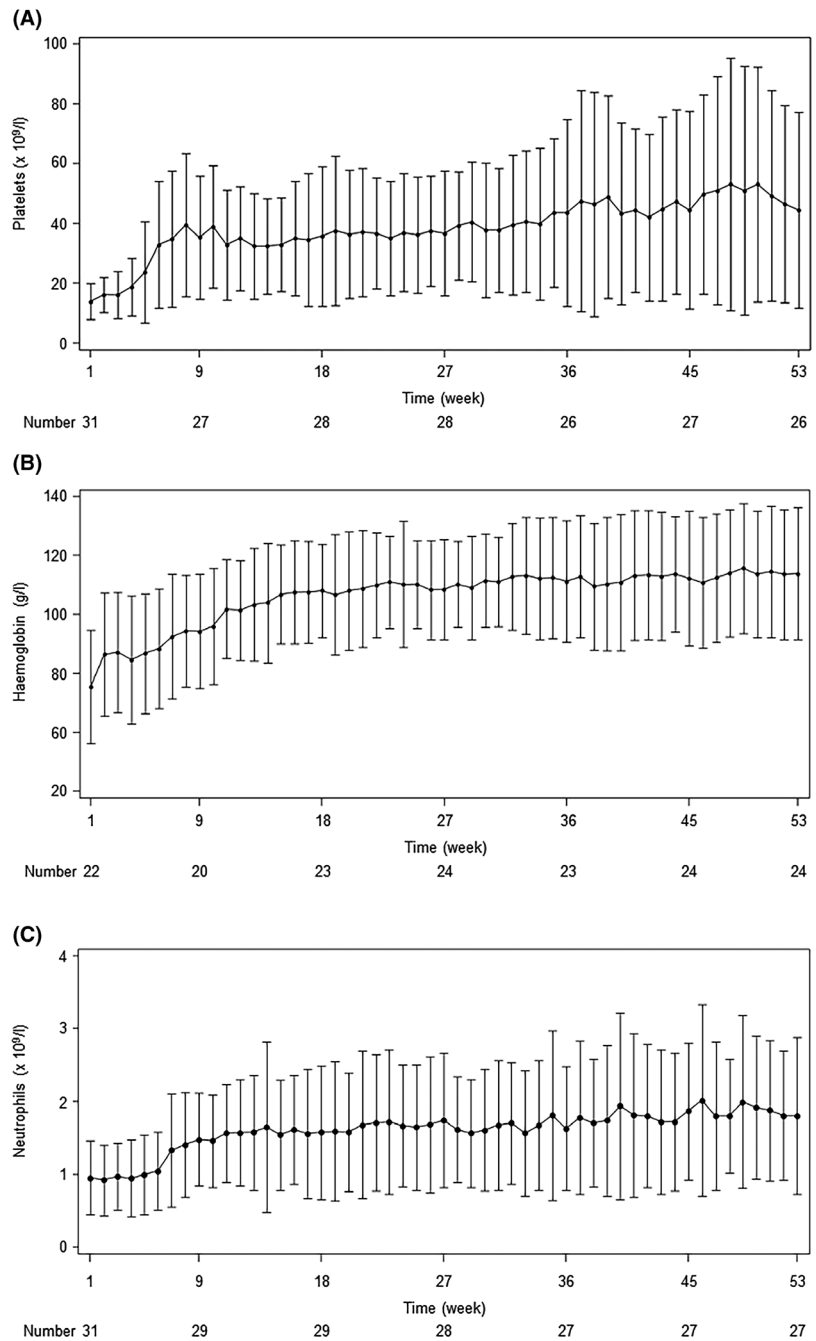


Fig 3. Change in haematological parameters with romiplostim. Data are given as mean (\pm SD) during treatment with romiplostim (5–20 $\mu\text{g}/\text{kg}$) for 52 weeks: (A) platelet count, (B) haemoglobin concentration and (C) neutrophil count ($N = 31$).

alanine aminotransferase (ALT) increased and γ -glutamyl-transferase increased). Two patients showed increases in reticulins (from Grade 0 to 1) by the end of treatment, which were not considered as AEs.

One patient was positive for anti-romiplostim binding antibody prior to treatment, which was maintained during treatment. Another patient who was negative for anti-TPO antibody at baseline developed anti-TPO binding antibody at the end of treatment. Both patients were negative for neutralising antibodies.

Karyotype analysis showed abnormalities in two patients after romiplostim administration. In one patient, G-banding

analysis revealed 53, XX, +3, +4, +14, +16, +17, +19, +21[1]/46, XX[8] at week 27; treatment was continued and no abnormality was observed by G-banding (46, XX[12]) at week 53 and no abnormalities were detected by FISH analyses at any time. This result may therefore be artefactual. In the other patient, in whom treatment was discontinued because of no haematological response with romiplostim 20 $\mu\text{g}/\text{kg}$ at week 16, the abnormality was seen at the end of treatment. G-banding analysis revealed 45, XX, -7[4]/45, idem, del(5)(q?)[1]/46, XX[15]. FISH analysis of BM detected monosomy 7. At the baseline analyses, monosomy 7

Table IV. AEs during romiplostim treatment.

	No. of patients (%) [N = 31]
Any AE	29 (94)
Treatment-related* AE	17 (55)
Death	0
Serious AE	2 (7)
Treatment-related* serious AE	0
AE occurring in ≥ 3 patients by preferred term†	
Nasopharyngitis	13 (42)
Upper respiratory tract infection	8 (26)
Pyrexia	6 (19)
Headache	5 (16)
Diarrhoea	4 (13)
Muscle spasms	4 (13)
Abdominal pain upper	3 (10)
ALT increased	3 (10)
Back pain	3 (10)
Contusion	3 (10)
Influenza	3 (10)
Malaise	3 (10)
Pain in extremity	3 (10)
Oropharyngeal pain	3 (10)
Treatment-related* AE occurring in ≥ 2 patients by preferred term†	
Headache	4 (13)
Muscle spasms	4 (13)
ALT increased	2 (6)
Fibrin D-dimer increased	2 (6)
Malaise	2 (6)
Pain in extremity	2 (6)

AE, adverse event; ALT, alanine aminotransferase.

*Considered by the investigator as possibly or related to treatment.

†Coded by MedDRA version 20.1.

was not detected either by G-banding (46, XX[3]) or by FISH analysis. BM examination showed no dysplasia in morphology. None of 31 patients showed transformation to myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) during the study.

Pharmacokinetics

The pharmacokinetic parameters for romiplostim at weeks 1 and 4 after the administration of romiplostim 10 $\mu\text{g}/\text{kg}$ once weekly are summarised in Table S3 and the corresponding serum romiplostim concentration-time profiles are shown in Figure S5. Pharmacokinetic parameters were similar at week 4 and accumulation ratios for maximum serum romiplostim concentration (C_{max}), area under the serum romiplostim concentration-time curve from time 0 to t (AUC_{0-t}) and minimum serum romiplostim concentration (C_{min}) were close to unity (0.8–1.2). Mean serum C_{min} for romiplostim was about 0.4–0.5 $\mu\text{g}/\text{l}$ for the first 4 weeks when romiplostim dose was fixed at 10 $\mu\text{g}/\text{kg}$ once weekly and subsequently increased to about 0.65 $\mu\text{g}/\text{l}$ during long-term

treatment to week 41 when romiplostim dose was titrated (5–20 $\mu\text{g}/\text{kg}$) once weekly (most patients received 20 $\mu\text{g}/\text{kg}$) (Figure S6).

Discussion

In the present study, we assessed the proportion of patients achieving haematological response to romiplostim in patients with AA refractory to IST using romiplostim at 10 $\mu\text{g}/\text{kg}$ as a starting dose based on our previous dose-finding study.⁷ The primary endpoint of any haematological response at week 27 was 84%. It was higher than the expected rate of 40%, which was based on the haematological response at 3–4 months with eltrombopag in 43 patients with IST-refractory AA.⁶ The response rate in the present study was also higher than that of our previous romiplostim study,⁷ a French retrospective romiplostim study¹³ and the reference eltrombopag study,⁶ suggesting that a higher initial dose of romiplostim may be required for effective HSPC stimulation in patients with AA.

The response criteria used to determine haematological response were similar between the romiplostim and eltrombopag studies, and both used doses titrated within a broad range. There were differences between the studies in the populations recruited. Patients with severe AA refractory to IST were exclusively recruited in the eltrombopag study and all had received previous ATG,⁶ while 42% of patients in our present study had severe/very severe AA. Not all the patients in our present study had received prior ATG (26% of patients had received cyclosporin monotherapy). Non-severe AA populations can differ regarding pathophysiology or degree of HSPC deficit, which may affect treatment outcome.¹⁴ *Post hoc* analysis of any haematological response at week 27 in our present study to allow comparison across the studies, revealed no significant difference comparing patients with non-severe and those with severe/very severe AA (94% vs. 69%, $P = 0.133$). Nevertheless, the 69% haematological response rate in the patient subgroup with severe/very severe AA in our present study remained higher than the 40% haematological response rate reported for eltrombopag.⁶ *Post hoc* analysis of any haematological response at week 27 also revealed no significant difference comparing patients who had previously received ATG plus cyclosporin and those who had received cyclosporin monotherapy (77% vs. 100%, $P = 0.286$). Ethnicity was exclusively Asian in our present study, but there was only one Asian in the eltrombopag study, which was primarily White, Black or Hispanic. The differences in study population may, at least in part, account for the different response to romiplostim and eltrombopag. Although both romiplostim and eltrombopag act via a common mechanism of action as TPO mimetics, they do exhibit different actions. Eltrombopag has been shown to stimulate haematopoiesis at the stem cell level through iron chelation-mediated molecular re-programming, whereas romiplostim does not exhibit iron-chelating activity.¹⁵ Furthermore, the

agents have different locations for TPO-receptor binding: romiplostim binds to the extracellular region of the receptor and eltrombopag to the transmembrane region.¹⁶

At the end of the study, week 53, 12 (39%) patients had achieved a trilineage response and 20 (65%) patients had achieved a platelet response. A similar platelet response rate of 55% was reported in the Phase II study of romiplostim among 33 patients with AA refractory to IST.⁷ Of note, robust trilineage response (39%) in the present study is higher than that reported in our previous Phase II study (15%, five of 33). This improvement may be, in part, accomplished by initiating treatment with high-dose romiplostim, which may be important for stem cell stimulation to achieve a robust response in patients with AA. Recently, it has been reported that a 150 mg starting dose of eltrombopag resulted in a better response than 50 mg (40% vs. 50%).¹⁷ All these data suggest that early and more prolonged administration of TPO-receptor agonists at high doses may hasten haematological response. The trilineage response rate at week 53 (39%) was increased compared to that at week 27 (26%), indicating a reinforced robust haematopoiesis over this period.

Safety data from the present study demonstrated that romiplostim was well tolerated. No patients developed neutralising antibodies to romiplostim or TPO during treatment, which is in agreement with our previous study of romiplostim.⁷ None of the patients showed transformation into MDS or AML. Karyotype analysis of BM revealed development of monosomy 7 in one patient, who was discontinued at week 16 because of no response for 8 weeks. Development of new cytogenetic abnormalities has been raised as a concern with eltrombopag since eight of 43 (19%) patients with AA treated for 3–13 months developed clonal evolution.⁶ A previous study of romiplostim in 35 patients with AA revealed that no patients developed clonal evolution after treatment for up to 3 years.⁷ The reason for the differences related to clonal evolution between romiplostim and eltrombopag is unclear. It may be related to differences in ethnicity, patient characteristics or activation of the signalling pathway (see above for differences between the TPO-receptor agonists), which may promote expansion of dormant pre-existing clones with an aberrant karyotype.

A limitation of the present study was the recruitment of a relatively small number of patients, as well as the inclusion of a somewhat heterogeneous patient population with respect to their disease severity. However, recruitment of patients with refractory AA is restricted given the rarity of the condition. Long-term follow-up data will be required to confirm the durability of response and monitor for potential clonal evolution.

In conclusion, the use of a higher starting dose of romiplostim followed by dose titration was effective and well tolerated in the treatment of patients with AA refractory to IST. We are conducting a single-arm, open-label combination study of romiplostim with standard IST (ATG plus cyclosporin) as first-line treatment in severe AA (clinicaltrials.gov, NCT03957694).

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Author contributions

Jun Ho Jang, Kouki Enokitani, Kinuko Mitani, Jong Wook Lee and Shinji Nakao contributed to the study design. Jun Ho Jang, Yoshiaki Tomiyama, Koji Miyazaki, Koji Nagafuji, Kensuke Usuki, Nobuhiko Uoshima, Tomoaki Fujisaki, Hiroshi Kosugi, Itaru Matsumura, Ko Sasaki, Masahiro Kizaki, Masashi Sawa, Michihiro Hidaka, Naoki Kobayashi, Satoshi Ichikawa, Yuji Yonemura and Jong Wook Lee collected data for the study. Jun Ho Jang, Kouki Enokitani, Kinuko Mitani, Jong Wook Lee and Shinji Nakao participated in the analysis and interpretation of the data, and writing the manuscript. All authors reviewed the manuscript, approved the final version and support this publication.

Conflict of interest

Yoshiaki Tomiyama honoraria from Novartis Pharma K.K., Chugai Pharmaceutical Co., Ltd. and Kyowa Kirin Co., Ltd.; and advisory committee member for Novartis Pharma K.K. Koji Miyazaki honoraria from Kyowa Kirin Co., Ltd., Chugai Pharmaceutical Co., Ltd., Pfizer Japan, Inc., Novartis Pharma K.K., Novo Nordisk Pharma Ltd., KM Biologics, Nihon Pharmaceutical Co., Ltd. and CSL Behring K.K.; and research funding from Kyowa Kirin Co., Ltd., Chugai Pharmaceutical Co., Ltd., Pfizer Japan Inc., Daiichi Sankyo Co., Ltd., Astellas Pharma Inc., Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd. and MSD K.K. Kensuke Usuki research funding from Astellas Pharma Inc., Alexion Pharmaceuticals, AbbVie GK, Gilead, Symbio Pharmaceuticals Ltd., Daiichi Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Chugai Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Novartis Pharma K.K., Bristol-Myers Squibb Company, Ono Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Celgene Corporation, Takeda Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Mundipharma K.K., Astellas-Amgen-Biopharma KK, Apellis Pharmaceuticals Inc, Nippon Shinyaku Co., Ltd., Kyowa Kirin Co., Ltd. and Pfizer Japan Inc.; and speakers bureaus for Novartis Pharma K.K., Alexion Pharmaceuticals, Eisai Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., MSD K.K., Otsuka Pharmaceutical Co., Ltd., Symbio Pharmaceuticals Ltd., Celgene Corporation, Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., Nippon Shinyaku Co., Ltd., PharmaEssentia

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supplementary Methods.

Data S2. Study Protocol.

Table S1. Dose tapering and discontinuation.

Table S2. Bone marrow cellularity.

Table S3. Pharmacokinetic parameters for romiplostim.

Fig S1. Treatment interruption or dose reduction due to excessive platelet increase.

Fig S2. Kaplan–Meier plot of time to haematological response.

Fig S3. Kaplan–Meier plot of time to trilineage response.

Fig S4. Kaplan–Meier plot of the duration of haematological response.

Fig S5. Serum romiplostim concentration-time profile.

Fig S6. Serum trough romiplostim concentration over time.

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