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ORIGINAL PAPER

Haematopoiesis

Romiplostim with ciclosporin A in patients with aplastic anaemia naïve to immunosuppressive therapy: A phase 2/3 study

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Summary

Romiplostim has been shown to restore multi-lineage haematopoiesis and is effective in patients with aplastic anaemia (AA) refractory to immunosuppressive therapy (IST). This open-label, phase 2/3 study (NCT04095936) recruited adult AA patients in Japan and Korea who had not received prior IST and evaluated the efficacy and safety of romiplostim plus ciclosporin A (CsA). Romiplostim was initiated at 10 μg/kg once weekly through Week 4 and adjusted between 0 and 20 μg/kg from Week 5 onwards. CsA was administered at 5–6 mg/kg/day in two divided doses through Week 26. A total of 24 patients (median [range] age, 52 [19–80] years) were enrolled, and 22 (91.7%) completed the study. Four patients (16.7%) had very severe AA (VSAA), 13 (54.2%) had severe AA (SAA) and seven (29.2%) had transfusion-dependent non-severe AA (NSAA). A haematological response at Week 27 was observed in 10/24 patients (overall response, 41.7%; 95% confidence interval, 22.1%–63.4%). At Week 27, the subgroup overall response rates were 0.0% in VSAA, 46.2% in SAA and 57.1% in NSAA. Nearly 92% of patients experienced at least one treatment-emergent adverse event (TEAE), but no drug-related Grade ≥3 TEAEs were reported. One patient

The results of this study were, in part, presented at the European Haematology Association Congress in Frankfurt, Germany, on 14–15 June 2023.

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developed myelodysplastic syndromes. Treatment with romiplostim plus CsA was effective and well tolerated in patients with AA who had not previously received IST.

KEYWORDS
aplastic anaemia, ciclosporin, immunosuppressive therapy, romiplostim, thrombopoietin

INTRODUCTION

Aplastic anaemia (AA) is characterised by a reduction or absence of haematopoietic precursors in bone marrow, leading to pancytopenia and decreased bone marrow cellularity (hypoplasia).[1,2] Treatment of AA includes supportive care, such as platelet or erythrocyte transfusion, as well as therapies aimed at restoring haematopoietic function, such as immunosuppressive therapy (IST), anabolic steroid therapy, and haematopoietic stem cell transplantation.[3,4] The choice of frontline therapy depends on factors such as patient age, disease severity, donor availability, and access to optimal treatment.[4,5]

Although anti-thymocyte globulin (ATG) is essential for IST in patients with severe AA (SAA),[6] an alternative therapeutic strategy for patients who cannot tolerate ATG is needed. Rabbit ATG administration necessitates hospitalisation for intravenous infusion over at least 6 h once daily for 5 days, with possible side effects including serum sickness.[7,8] Therefore, identifying an effective drug therapy for AA that does not rely on ATG is crucial. In clinical practice, the standard first-line treatment of AA is IST in combination with eltrombopag, a thrombopoietin (TPO) receptor agonist. While over 70% of patients respond to this regimen, some are unable to tolerate it or fail to achieve a response.

Romiplostim, a thrombopoiesis-stimulating agent, exerts its effects by binding to and activating the TPO receptor, also known as the myeloproliferative leukaemia protein, thereby triggering intracellular transcriptional pathways.[9] Romiplostim promotes platelet production by stimulating TPO receptor-mediated proliferation and differentiation of megakaryocyte precursors in the bone marrow.[10–13] Romiplostim is approved and used worldwide to treat immune thrombocytopenia and refractory AA.[14–17] Moreover, romiplostim has been reported to enhance response rates in AA patients refractory to eltrombopag.[18] Because eltrombopag and romiplostim have different mechanisms of action, romiplostim may be an alternative front-line treatment option for AA.

A recent phase 2/3 study demonstrated that romiplostim is effective in restoring blood cell counts in patients with AA who are refractory to, or ineligible for, IST,[9] suggesting that romiplostim plus ciclosporin A (CsA) may offer a therapeutic benefit in ATG-naïve patients. Accordingly, this phase 2/3 clinical trial was conducted to evaluate the efficacy, safety and pharmacokinetics of romiplostim in patients with AA who had not previously received IST.

METHODS

Patients

This phase 2/3 study included patients with AA from Japan (≥20 years) and Korea (≥19 years) who required IST. Inclusion and exclusion criteria are provided in the Supporting Information text.

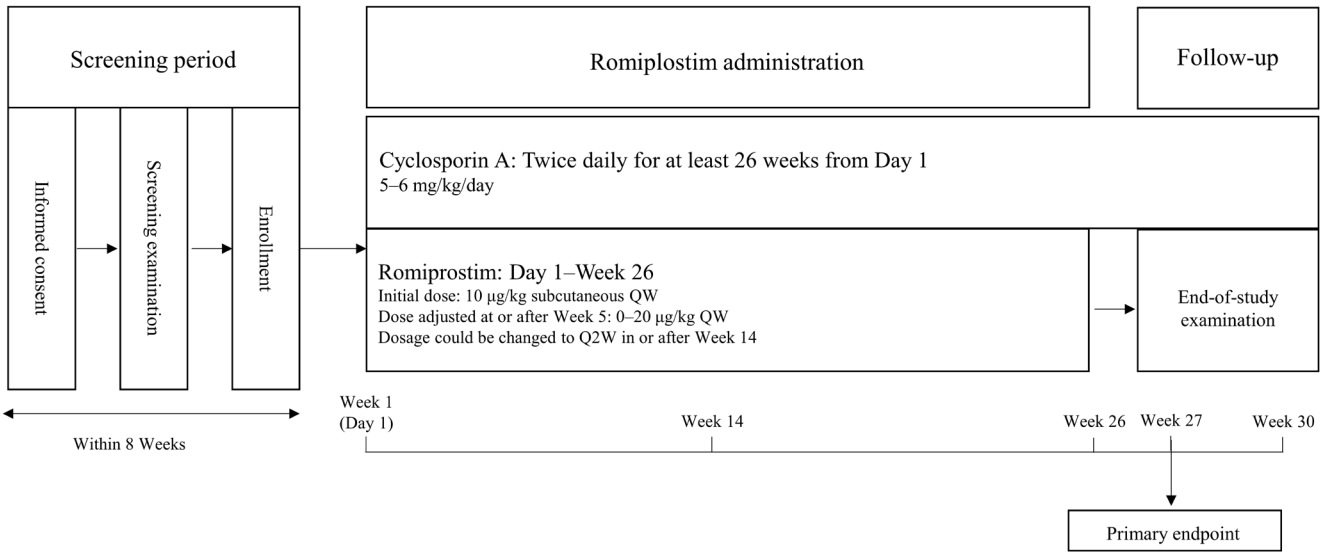


FIGURE 1 Study design. Q2W, biweekly; QW, once weekly.

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Study design and intervention

This multinational, open-label, phase 2/3 study with an intra-patient dose adjustment of romiplostim comprised a screening period, treatment period, and follow-up period (Figure 1). Patients underwent the end-of-study examination at Week 30 and completed the study. No randomisation or blinding procedure was used.

Romiplostim was started at 10 μg/kg once weekly; the dose was fixed from Day 1 to Week 4. From Week 5 onwards, the dose was adjusted between 0 and 20 μg/kg, according to the criteria described in the Supporting Information text, to obtain an adequate haematological response. When the 531–004 response assessment criteria for complete response (CR) were met for 4 consecutive weeks on or after Week 14, the dose of romiplostim was changed to once every 2 weeks. Thereafter, the dosage was maintained if the criteria for CR were met with no safety concerns. Patients received CsA at a daily initial dose of 5 or 6 mg/kg in two divided doses, at least from Day 1 to Week 26, which could be interrupted at any time for safety reasons. CsA plasma levels were not evaluated.

The study was conducted after obtaining ethical approval from the institutional review boards, per the principles described in the Declaration of Helsinki, and in compliance with the good clinical practice guidelines of the International Conference on Harmonisation and all applicable domestic and local laws. This clinical trial is registered with ClinicalTrials.gov (NCT04095936).

Efficacy outcomes

The primary efficacy end-point was the achievement of overall response (OR) defined as CR plus partial response (PR) of the haematological response at Week 27 (Table S1). The secondary efficacy end-points were: OR at Week 14, time to OR at each evaluation time point until Week 27, the duration of haematological response until Week 27 and maximum duration during which OR was continuously achieved until Week 27; decrease in platelet or erythrocyte transfusion requirements/platelet or erythrocyte transfusion independence at Week 27 (Supporting Information text; Table S2); and changes from baseline in platelet count, haemoglobin concentration, neutrophil count and reticulocyte count at each evaluation time point until Week 27.

Safety

The safety outcomes in terms of adverse events (AEs) for the safety analysis set included treatment-emergent AEs (TEAEs), drug-related TEAEs (TEAEs for which a causal relationship with romiplostim was assessed as 'related'), Grade ≥3 TEAEs and serious AEs (SAEs) (Supporting Information text). Other safety outcomes included clinical laboratory data, vital signs, standard 12-lead electrocardiograms, transformation into acute myeloid leukaemia and/or myelodysplastic syndromes (MDS), bone marrow cellularity and reticulin and paroxysmal nocturnal haemoglobinuria-type blood cells. All patients were tested for anti-romiplostim antibody and TPO antibodies at Weeks 1, 13 and 27. Reticulin grade was assessed at baseline and Week 27. Chromosomal abnormalities were evaluated using G-banding and fluorescence in situ hybridisation analyses.

Pharmacokinetics and immunogenicity end-point

The pharmacokinetics and immunogenicity end-points are expressed as serum romiplostim concentration, anti-romiplostim antibody and anti-TPO antibody respectively.

Statistical methods

A meta-analysis of ATG and CsA indicated a response rate of approximately 50% at 6 months.[19] The expectation was that the combination of CsA and romiplostin would yield a similar response rate while achieving a threshold of 20% higher than the monotherapy response rate of 17.9% observed with ATG.[20] To achieve this, a sample size of 24 patients was determined to provide over 80% power for the study.[19] To achieve a SAA to very severe AA (VSAA) patient ratio of at least ≥70%, the number of patients diagnosed with non-severe AA (NSAA, AA that did not meet the criteria for SAA/VSAA) at enrolment was not expected to exceed seven in both Japan and Korea. The response rate after 6 months of ATG/CsA treatment in ATG-naive AA patients ranged from 33% to 57%, while that in Japan was 17.9% at 6 months.[20] Therefore, for the present study, the threshold proportion was set at 20%.

Descriptive statistics were used to summarise categorical data and continuous variables. A two-sided p-value of <0.05 was considered significant. All analyses were performed using Covance's SAS Environment (Version 9.4 or later) of the SAS® statistical software (SAS Institute Inc., Cary, NC, USA).

The preplanned analytical populations were (a) the full analysis set, including all enrolled patients except those who had never been exposed to romiplostim and those without evaluable efficacy variables, that is, platelet count, haemoglobin concentration, neutrophil count or reticulocyte count after romiplostim administration; (b) the safety analysis set, including all enrolled patients except those who had never been exposed to romiplostim; and (c) the pharmacokinetic analysis set, including all enrolled patients except those who had never been exposed to romiplostim and never underwent pharmacokinetic blood sampling after romiplostim administration.

RESULTS

The disposition of patients and reasons for withdrawal are illustrated in Figure S1. Thirty-one patients were screened and

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24 (nine from Japan and 15 from Korea) were enrolled. All 24 patients were included in all the analysis sets, 22 (91.7%) patients completed the treatment period and two (from Korea) discontinued treatment (one due to AEs and the other due to death after romiplostim discontinuation).

At the time of enrolment, the median age of the patients was 52 (range, 19–80) years; most patients (75.0%) were aged <65 years; 58.3% of patients were female (Table 1). The median time since diagnosis was 24.0 (range, −8 to 7374) days. Regarding AA severity, four (16.7%) patients had VSAA, 13 (54.2%) had SAA and seven (29.2%) had NSAA.

For the primary end-point, the OR was 29.2% (7/24, 95% confidence interval [CI], 12.6%–51.1%) at Week 14 and 41.7% (10/24, 95% CI, 22.1%–63.4%) at Week 27 (Table 2). The haematological responses according to the severity subgroup were 0/4 (0%), 6/13 (46.2%) and 4/7 (57.1%) patients in the VSAA, SAA and NSAA groups, respectively, achieving OR at Week 27. At Week 27, the ORs were 58.3% (7/12 patients) and 25.0% (3/12 patients) for patients with baseline reticulocytes ≥0.02/L and <0.02/L, respectively; and 44.4% (8/18 patients) for patients aged <65 years and 33.3% (2/6 patients) for those aged ≥65 years (Table S3). In addition, the duration of haematological response until Week 27 was investigated; the mean ± SD value of maximum duration of response was 92.2 ± 39.9 days.

At Week 27, 14/19 (73.7%) patients who received platelet transfusion prior to the first dose of romiplostim had decreased platelet transfusion requirements, whereas eight (42.1%) achieved platelet transfusion independence (Table 3).

TABLE 1 Baseline characteristics of patients at the time of enrolment (safety analysis set).

Characteristic	Total ($N=24$)
Median (range) age, years	52 (19–80)
Female/male, *n* (%)	14/10 (58.3/41.7)
Asian ethnicity, *n* (%)	24 (100.0)
Median (range) body mass index, kg/m^2	24.3 (16.7–31.8)
Median (range) time since diagnosis,[a] days	24.0 (−8 to 7374)
Aplastic anaemia severity, *n* (%)	
Non-severe	7 (29.2)
Severe	13 (54.2)
Very severe	4 (16.7)
ECOG score 0/1, *n* (%)	12/12 (50.0/50.0)
Prior transfusion required, *n* (%)	
Platelets	19 (79.2)
Red blood cells	22 (91.7)
Median (range) platelet count, /L	0.0115 (0.001–0.039)
Median (range) neutrophil count, /L	0.000453 (0.000028–0.00195)
Median (range) reticulocyte count, /L	0.020957 (0.0025–0.1573)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

[a]Four patients were definitively diagnosed with aplastic anaemia after enrolment.

At Week 27, 15/22 (68.2%) patients who received erythrocyte transfusion prior to the first dose of romiplostim had decreased erythrocyte transfusion and nine (40.9%) achieved erythrocyte transfusion independence.

The mean platelet count increased to a maximum of 0.069385 ± 0.077894/L ($n=13$) at Week 8 and was 0.054000 ± 0.040792/L ($n=16$) at Week 27 (Figure 2A). The mean haemoglobin concentration increased to a maximum of 11.37 ± 1.77 g/dL ($n=3$) at Week 2 and was 10.39 ± 1.89 g/dL ($n=12$) at Week 27 (Figure 2B). The mean reticulocyte count increased to a maximum of 0.076647 ± 0.041870/L ($n=20$) at Week 23 and was 0.070128 ± 0.035350/L ($n=22$) at Week 27 (Figure 2C). The mean neutrophil count increased to a maximum of 0.001716 ± 0.000899/L ($n=17$) at Week 10 and was 0.001552 ± 0.000846/L ($n=21$) at Week 27 (Figure 2D).

Overall, 22/24 (91.7%) patients experienced at least one TEAE, and three (12.5%) patients experienced at least one drug-related TEAE as judged by the investigator. The most frequently reported TEAEs were nausea (7/24 patients, 29.2%); headache (6/24, 25.0%); dyspepsia (5/24, 20.8%); abdominal pain and hypomagnesaemia (4/24, 16.7% each); and arthralgia, constipation and diarrhoea (3/24, 12.5% each) (Table 4). The drug-related TEAEs were nausea, liver function test abnormal and coagulation test abnormal which occurred in one patient (4.2%) each.

TEAEs Grade ≥3 were reported in nine (37.5%) patients; the most common was febrile neutropenia (2/24, 8.3%) (Table S4). No drug-related Grade ≥3 TEAEs were reported. Of the 17 patients with VSAA/SAA, two (11.8%) experienced AEs related to the romiplostim + CsA combination. Drug-related AEs were reported in 0% (0/4) patients with VSAA, 15.4% (2/13) patients with SAA and 14.3% (1/7) patients with NSAA.

The TEAEs leading to death were pneumonia and pneumonia fungal (one patient; 5.9% each), which were considered unrelated to romiplostim. Other serious TEAEs occurred in seven patients (29.2%); none were considered related to romiplostim. The SAE of MDS that occurred in one patient (4.2%) was considered related to romiplostim by the sponsor. No other significant TEAEs were reported.

No chromosomal abnormality was detected by fluorescence in situ hybridisation analyses for chromosome 7. G-banding revealed no chromosomal abnormalities at screening. Chromosomal abnormalities were observed in three patients at Week 27. In the first patient, 46, Y, add(X)(q22), −4, +mar [1] and 46, XY [19] were detected in 20 dividing cells, and the investigator considered this abnormality to be unrelated to treatment with romiplostim. The second patient had 46, XX, t(12;20)(q21;q11.2) [6] and 46, XX [14] in 20 dividing cells, and the investigator considered that the clinical significance of this abnormality was unknown. The third patient (4.2%) had 46, XX, del(13)(q12q22) [6] and 46, XX [14] in 20 dividing cells, and the investigator reported this patient for the SAE of MDS. The Efficacy and Safety Assessment Committee concluded that this chromosomal abnormality was likely to be related to MDS. This patient showed no response at Week 27 and their haematological

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TABLE 2 Haematological response according to severity subgroup at Weeks 14 and 27.

	VSAA ($n=4$)	SAA ($n=13$)	NSAA ($n=7$)	VSAA + SAA ($n=17$)	Total
Response assessment at Week 14					
Response, *n* (%)					
CR	0 (0.0)	1 (7.7)	1 (14.3)	1 (5.9)	2 (8.3)
PR	0 (0.0)	2 (15.4)	3 (42.9)	2 (11.8)	5 (20.8)
NR	4 (100.0)	10 (76.9)	3 (42.9)	14 (82.4)	17 (70.8)
Overall response (CR + PR)	0 (0.0)	3 (23.1)	4 (57.1)	3 (17.6)	7 (29.2)
95% confidence interval	0.0, 60.2	5.0, 53.8	18.4, 90.1	3.8, 43.4	12.6, 51.1
Response assessment at Week 27					
Response, *n* (%)					
CR	0 (0.0)	0 (0.0)	3 (42.9)	0 (0.0)	3 (12.5)
PR	0 (0.0)	6 (46.2)	1 (14.3)	6 (35.3)	7 (29.2)
NR	4 (100.0)	7 (53.8)	3 (42.9)	11 (64.7)	14 (58.3)
Overall response (CR + PR)	0 (0.0)	6 (46.2)	4 (57.1)	6 (35.3)	10 (41.7)
95% confidence interval	0.0, 60.2	19.2, 74.9	18.4, 90.1	14.2, 61.7	22.1, 63.4

Abbreviations: CR, complete response; NR, no response; NSAA, non-severe aplastic anaemia; PR, partial response; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia.

TABLE 3 Summary of independence of transfusion at Week 27 from baseline (full analysis set).

	Total ($N=24$) *n* (%)
Platelet transfusion dependence at baseline	19 (79.2)
Independence of platelet transfusion	8 (42.1)[a]
Erythrocyte transfusion dependence at baseline	22 (91.7)
Independence of erythrocyte transfusion	9 (40.9)[a]

[a]Denominators for percentages of platelet and erythrocyte transfusion are based on the number of patients with platelet and erythrocyte transfusion dependence at baseline, respectively.

parameters are shown in Table S5. There were no transformations into acute myeloid leukaemia. Overall, there was no significant difference in the incidence of TEAEs between Japan and Korea, confirming acceptable safety in patients of both countries.

Mean trough serum concentrations of romiplostim increased initially and remained almost constant after Week 4 (range: 1297.05–1601.83 pg/mL). One patient tested positive for anti-romiplostim binding antibodies at Week 27 but tested negative for anti-romiplostim neutralising antibodies. One patient tested positive for anti-TPO-binding antibodies at Week 1 but tested negative for anti-TPO-neutralising antibodies.

DISCUSSION

This study was the first of its kind to assess the efficacy of romiplostim in combination with CsA in patients in Japan and Korea with AA who were not previously treated with IST. The efficacy of romiplostim was demonstrated, with 10 patients achieving a CR or PR at Week 27, resulting in an OR of 41.7% (95% CI, 22.1%–63.4%). Notably, the lower limit of the 95% CI exceeded the prespecified threshold value of 20%. Because the OR of the combination of romiplostim + CsA in NSAA patients was 57.1% in the present study, we believe that this two-drug combination therapy can be considered as a new treatment option for patients with less severe disease or those who are ineligible for, or intolerant to, ATG. However, this combination of romiplostim + CsA may not be recommended over ATG-including regimens for VSAA or SAA patients because of the relatively low OR of 35.3% at Week 27 (Graphical Abstract).

A previous retrospective study found a CR and OR of 27.3% and 60.6%, respectively, at 6 months in patients treated with eltrombopag + CsA,[21] which are higher than those observed in the current study at Week 27 (CR 12.5% and OR 41.7%). The difference may be attributed to variations in the study design, such as the use of eltrombopag versus romiplostim, differences in CsA dosage or differences in the prevalence of paroxysmal nocturnal haemoglobinuria (PNH) clones and gene mutations, which were not evaluated in this study.[21]

In the SOAR (Activity and safety of Eltrombopag in combination with cyclosporin A as first-line treatment of adults with severe aplastic anaemia) study,[22] treatment-naïve patients with SAA received eltrombopag + CsA for 6 months, with responders continuing CsA therapy for an additional 18 months. The OR by and at 6-month in SAA patients was 46% and 37.0% respectively. In our study, the OR at Week 27 was 41.7%, which is comparable to the OR at 6 months (37.0%) reported in the SOAR study. Both studies had a comparable incidence of Grade ≥3 AEs. Common TEAEs observed in our study included nausea (29.2%), headache (25.0%) and dyspepsia (20.8%). Aside

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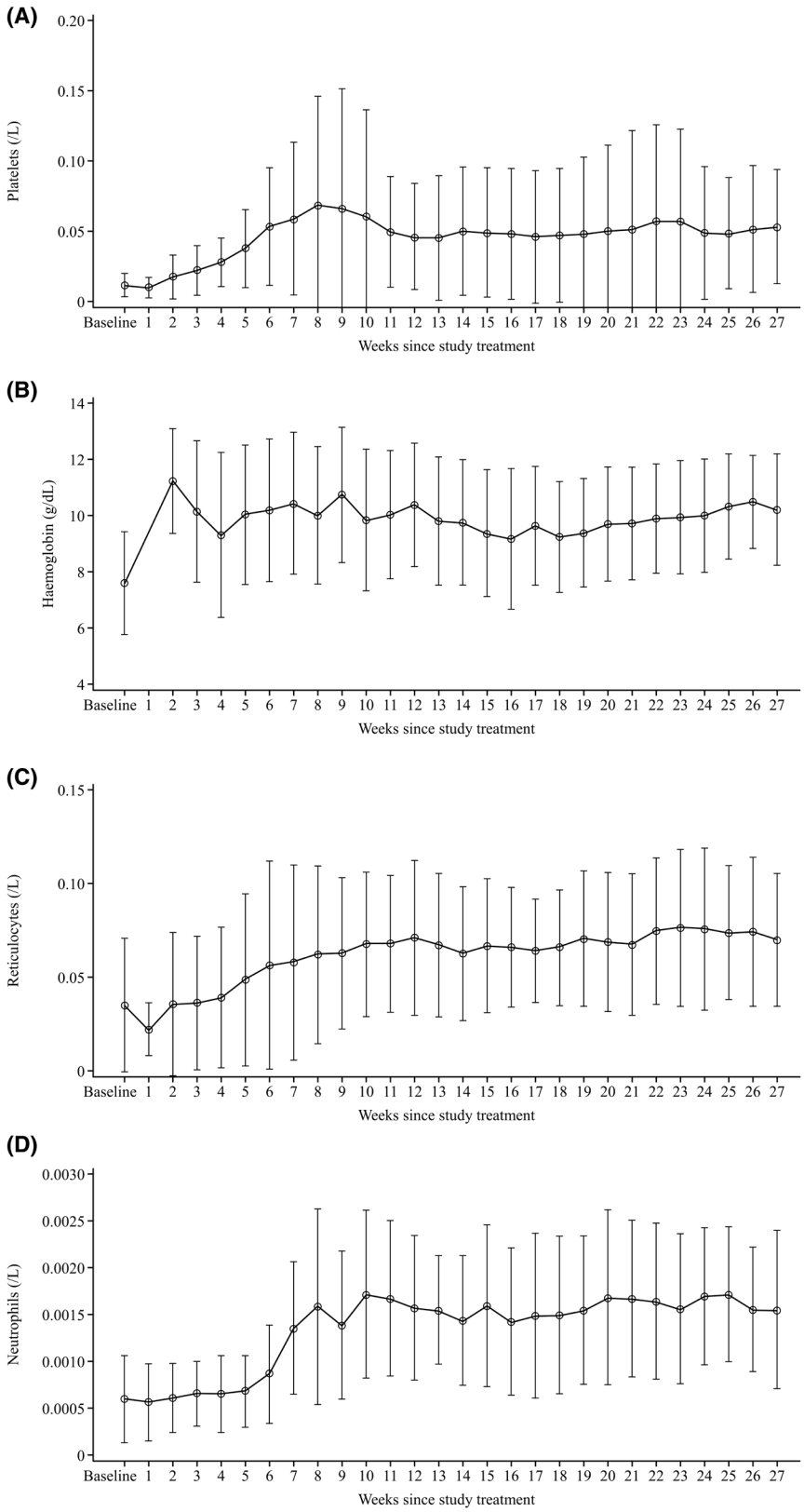


FIGURE 2 Change in haematological parameters throughout the study (mean ± standard deviation) (A) platelet count, (B) haemoglobin concentration, (C) reticulocyte count and (D) neutrophil count.

from nausea (30%) and diarrhoea (22%), the SOAR study also reported increased serum bilirubin (41%) and alanine aminotransferase concentration (22%).[22] Our study's outcomes are similar to those found in the SOAR study. In contrast, our results are inferior to other studies in which ATG combined with CsA and eltrombopag demonstrated

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TABLE 4 Summary of TEAEs with an incidence of ≥10% in the safety analysis set.

	Total ($N=24$)
	n (%)
Patients with any TEAE	22 (91.7)
Gastrointestinal disorders	14 (58.3)
Nausea	7 (29.2)
Dyspepsia	5 (20.8)
Abdominal pain	4 (16.7)
Constipation	3 (12.5)
Diarrhoea	3 (12.5)
Metabolism and nutrition disorders	6 (25.0)
Hypomagnesaemia	4 (16.7)
Musculoskeletal and connective tissue disorders	7 (29.2)
Arthralgia	3 (12.5)
Nervous system disorders	7 (29.2)
Headache	6 (25.0)

Note: *n* indicates the number of patients in each category. Percentages were calculated as 100 × (*n*/*N*). This table contains counts of patients and lists only PTs with incidences ≥10%. If a patient experienced more than one episode of an adverse event, the patient was counted only once within a PT. If a patient experienced >1 adverse event within a SOC, the patient was counted once for each PT and once for the SOC.

Abbreviations: PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

superior ORs,[23] which were further supported by findings from the RACE (Randomized Multicenter Trial Comparing Horse ATG plus Cyclosporine with or without Eltrombopag as First-Line) study.[24] Therefore, our findings suggest that romiplostim may serve as a viable option only in cases where ATG-based regimens are not feasible. Despite these limitations, our results reinforce the safety and efficacy of romiplostim as an alternative therapeutic option for SAA.

The incidence of chromosomal abnormalities in this study was consistent with those previously reported in studies from Japan and Korea, which reported abnormalities of chromosome 7 in 0/17[25] and 1/31[9] patients after romiplostim administration. Imada et al. observed a similar lower incidence of cytogenetic abnormalities in 1/11 patients treated with ATG/CsA and eltrombopag.[26] In contrast, Townsley et al. found the incidence of clonal cytogenetic evolution with the addition of eltrombopag to IST at 2 years was 8%, including 5.4% (5/92 cases) with chromosome 7 abnormalities.[23] Patel et al. recently reported that 5.7% of patients experienced clonal cytogenetic evolution over 4 years. While relapse and high-risk evolution rates were similar to historical controls, these events occurred earlier in patients treated with IST and eltrombopag.[27] Research has shown that clonal evolution among Japanese patients ranges from 3% to 5%, significantly lower than the 10–15% observed in patients from Western nations.[28,29] In Asian countries, the prevalence of secondary clonal disorders in patients treated with ATG/CsA may be lower than in patients in Western countries, regardless of the inclusion of TPO-RA.

Although three-drug combination therapy remains the preferred treatment approach for SAA and VSAA because of higher response rates, this study demonstrates that CSA + romiplostim, similar to CSA + eltrombopag, is a safe and effective alternative for patients who cannot receive ATG (OR: 57.1% in NSAA and 46.2% in SAA). Even in patients with severe disease, milder AEs were observed with romiplostim + CsA[18] than with the romiplostim + CsA + ATG regimen.[9] However, it should be noted that no efficacy was observed in patients with VSAA in this study. Because the use of ATG is associated with AEs, such as anaphylaxis and serum sickness,[7] this combination therapy could represent a new option for patients with less severe disease or those who are ineligible for, or intolerant to, ATG.

Limitations

This study had some limitations, such as its single-arm design. The generalisability of the results is difficult because of the inclusion of only Japanese and Korean patients, a relatively small sample size, and a limited follow-up period. CsA was administered from Day 1 to Week 26, but this study did not evaluate CsA plasma levels. We were unable to determine whether romiplostim + CsA therapy elicits a delayed response in patients who did not respond by Week 27 because these patients received ATG-containing regimens or other treatments following this study, in accordance with guidelines for AA treatment in Japan and Korea. The durability of the response of CsA + romiplostim was not evaluated in this study, and thus, future research should investigate this. Finally, this study did not determine the prevalence of PNH clones at baseline. Nearly half of the patients with AA could have small PNH clones at diagnosis.[30,31] PNH clones may have clinical implications for these patients as this can affect treatment response, thrombosis or evolution to haemolytic PNH, and thus should be included in future research.

CONCLUSIONS

This phase 2/3 study demonstrates the overall efficacy and safety of CsA combined with romiplostim in patients previously untreated with IST. No clinically significant TEAEs were reported, and the combination was found to be safe and tolerable as a first-line treatment for patients with AA. Further studies are needed to clarify the long-term efficacy of romiplostim and CsA combination therapy.

AUTHOR CONTRIBUTIONS

J. W. Lee, J. H. Jang, M. Noshiro, K. Mitani and S. Nakao contributed to the study design. J. W. Lee, J. H. Jang, A. Matsuda, K. Ozawa, K. Mitani, Y. Kanda and S. Nakao participated in the analysis and interpretation of the data

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and writing the manuscript. All authors reviewed the manuscript, approved the final version and supported this publication. J. H. Jang was responsible for the decision to submit the manuscript.

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DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed will be available in the Vivli repository, https://vivli.org/ourmember/kyowa-kirin/, as long as the conditions of data disclosure specified in the policy section of the Vivli website are satisfied.

TRIAL REGISTRATION

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SUPPORTING INFORMATION

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

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