Safety and efficacy of romiplostim in children with acquired aplastic anemia who are naïve to immunosuppressive therapy

Aplastic anemia (AA) is characterized by cytotoxic T-lymphocyte-mediated depletion of hematopoietic stem cells, resulting in pancytopenia and hypocellular bone marrow. The current standard of care for newly diagnosed or refractory severe AA combines immunosuppressive therapy (IST) (anti-thymocyte globulin [ATG] and cyclosporine) with the thrombopoietin receptor agonist (TPO-RA) eltrombopag.[1] However, treatment with IST plus eltrombopag has been less successful in children compared to adults.[2]

Romiplostim, another TPO-RA, has shown promise in adults with untreated and IST-refractory AA.[3,4] Pediatric data are limited to two small studies in children with severe AA that report modest efficacy in achieving overall and complete hematologic responses (CHR).[5,6] Given the limited data in children, this study aimed to assess the efficacy and safety of romiplostim in children with AA.

This single-arm study (Iranian Registry of Clinical Trials identifier 20221129056655N2) was approved by the Institutional Review Board of Shiraz University of Medical Sciences (Ethics code: IR.SUMS.MED.REC.1402.140). Written informed consent was obtained from the participants or their legal guardians. We consecutively enrolled patients aged <18 years with untreated severe/very severe AA or transfusion-dependent non-severe AA from October 2023 to January 2024. Participants received subcutaneous romiplostim (10 mcg/kg/week initially for 4 weeks, titrated to 20 mcg/kg/week, in increments of 5 mcg/kg/week from week 5-27) alongside IST (horse ATG 40 mg/kg/day × 4 days and cyclosporine 10 mg/kg/day). Romiplostim was started on the first day of ATG infusion. Dose adjustments were based on platelet response and toxicity, increasing every four weeks until a response was achieved. If the platelet count exceeded 200×10^9/L, the dose was reduced by one increment. Patients were followed monthly (every 4 weeks) for seven months (27 weeks), with a subset followed for an extended period of ten months (40 weeks). Romiplostim was tapered and discontinued upon achieving trilineage hematopoiesis sustained for eight weeks at the same romiplostim dose without transfusion. The definition of response criteria is summarized in *Online Supplementary Table S1*. The primary efficacy endpoints were the proportion of patients achieving trilineage response, CHR, and overall response (OR) at week 27. Secondary endpoints included the proportion of patients achieving trilineage response, CHR, and OR at week 40, and the proportion of patients who became transfusion-independent at weeks 27 and 40. Bone marrow aspiration, biopsy, and cytogenetic analysis were performed at baseline and at weeks 27 and 40 to evaluate for bone marrow fibrosis or clonal evolution. The study included 19 patients (12 males [63.2%], median age 6 years [range: 3-15 years], 17 with severe/very severe AA) who were followed for seven months (27 weeks), with 15 patients followed for an extended period of ten months (40 weeks). The median romiplostim dosage was 12 mcg/kg/week (range: 0-20 mcg/kg/week due to discontinuation in non-responders) at week 27 and 7 mcg/kg/week (range: 0-20 mcg/kg/week) at week 40 (*Online Supplementary Figure S1*). Significant improvements in hematologic parameters were observed during the 7-month follow-up (Figure 1A-C). Among the 15 patients followed for ten months, sustained improvements were noted, although changes after week 27 were not statistically significant (Table 1). At week 27, the proportion of patients achieving trilineage response and CHR was 47.4% (95% Confidence Interval [CI]: 24.4-71.1%) and 15.8% (95% CI: 3.4-39.6%), respectively. The overall response rate (ORR) at week 27 was 89.5% (95% CI: 66.9-98.7%). By week 40, the ORR remained high at 86.7% (95% CI: 59.5-98.3%), and the proportion with CHR improved to 20.0% (95% CI: 4.3-48.1%) (Figure 1D). Subgroup analysis revealed no significant differences in response rates in different severities of AA (Table 2). Eight patients (42.1%) were transfusion-dependent before starting romiplostim. Our center employs a conservative transfusion strategy (hemoglobin [Hb] <7 g/dL or platelets $<10\times10^9$/L in stable patients) to minimize the risk of alloimmunization for potential hematopoietic stem cell transplantation (HSCT). This accounts for the lower transfusion dependence rate. A total of 34 transfusions (platelet, packed red blood cells, or both) were recorded during the 40-week follow-up. Of these, 31 (91.2%) occurred in weeks 1-27, and only 3 (8.8%) occurred in weeks 28-40, representing an 82.4% reduction in transfusion rates. No transfusions were required during the final eight weeks. Six out of 8 patients (75%) became transfusion-independent at week 27. No patients remained transfusion-dependent at week 40, representing a 100% decrease in transfusion requirements compared to baseline (*Online Supplementary Figure S2*).

A few patients reported minor adverse events, including myalgia, headache, and abdominal pain. These were mild and transient, with no patients requiring drug discontinuation or dose reduction. No serious adverse events, bone marrow fibrosis, or clonal evolution were observed.

Our findings align with adult studies reporting hematologic responses to high-dose romiplostim (up to 20 mcg/kg/week) in IST-refractory AA.[3,7] Notably, lower doses (≤10 mcg/kg/week) yield inferior outcomes,[8] emphasizing the importance

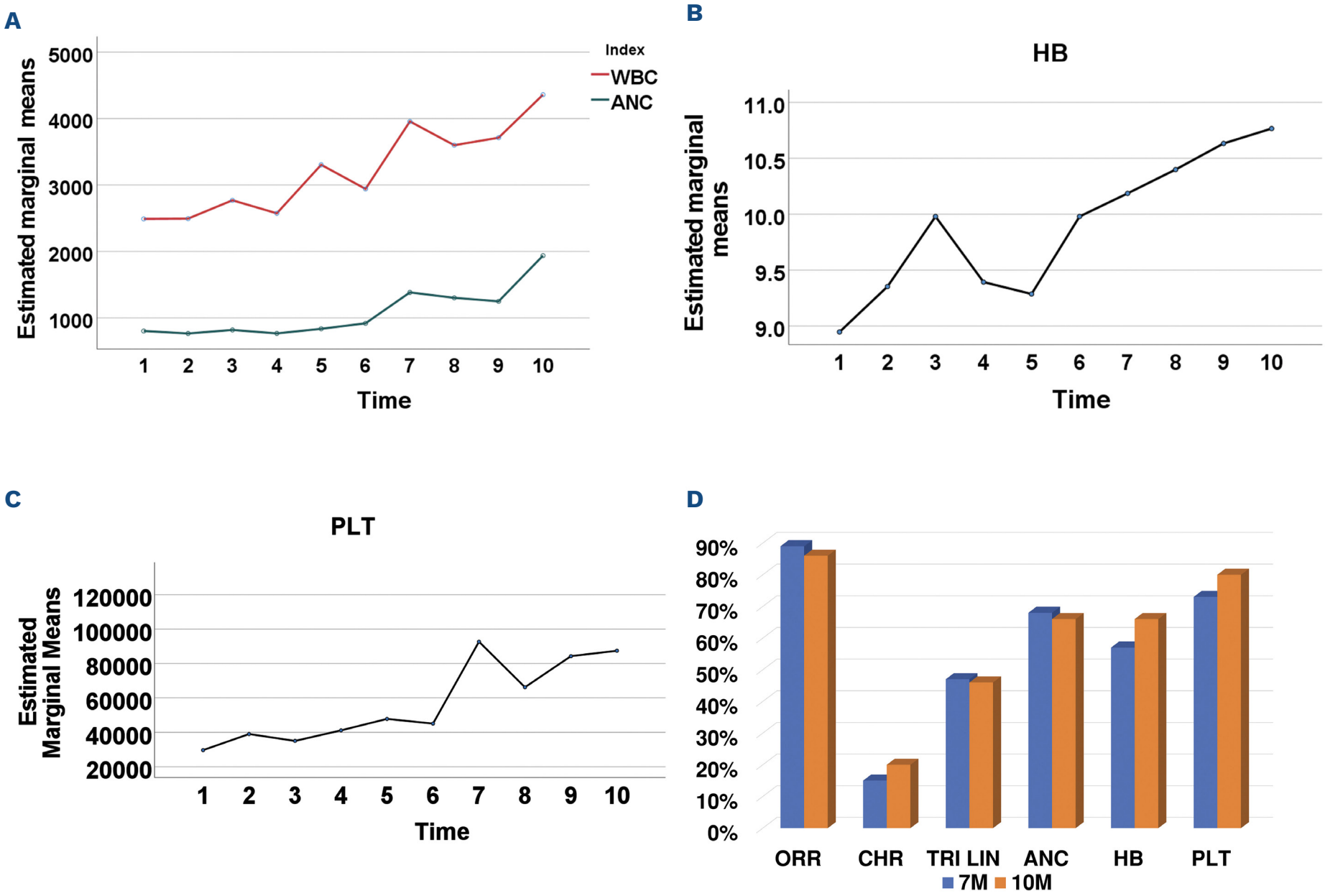

Figure 1. Hematologic responses following treatment with romiplostim. (A) Mean white blood cell (WBC) and neutrophil changes. (B) Mean hemoglobin (HB) changes. (C) Mean platelet (PLT) changes. (D) Overall hematologic response rates (ORR), trilineage (TRI LIN), and complete hematologic response rates (CHR), and response in different hematologic parameters. ANC: absolute neutrophil count.

Table 1. Baseline hematologic indices and their changes over 40 weeks of follow-up.

Hematologic index	Baseline N=19	Week 27 N=19	Week 40 N=15	*P1* Baseline and week 27	*P2* Baseline and week 40	*P3* Week 27 and week 40
Mean WBC, $\times 10^9$/L (95% CI) [Min-Max]	2.54 (2.02-3.07) [0.69-4.6]	4.19 (3.15-5.24) [1.46-9.7]	4.35 (3.44-5.26) [1.58-7.15]	< 0.001	< 0.001	0.175
Mean ANC, $\times 10^9$/L (95% CI) [Min-Max]	0.76 (0.51-1.01) [0.14-1.99]	1.52 (0.95-2.08) [0.44-4.75]	1.93 (1.15-2.72) [0.17-5.14]	< 0.001	< 0.001	0.366
Mean HB, g/dL (95% CI) [Min-Max]	9.0 (7.9-10.0) [5.0-12.6]	10.5 (9.5-11.5) [5.9-13.7]	10.7 (10.0-11.4) [9.2-12.9]	< 0.001	0.003	0.928
Mean PLT, $\times 10^9$/L (95% CI) [Min-Max]	28.10 (17.01-39.19) [4.0-80.0]	123.78 (59.51-188.06) [5.0-411.0]	87.40 (46.02-128.77) [18.0-248.0]	< 0.001	< 0.001	0.527
Mean absolute reticulocyte count, $\times 10^9$/L [Min-Max]	24.73 [0.31-7.23]	-	-	-	-	-

ANC: absolute neutrophil count; CI: Confidence Interval; HB: hemoglobin; N: number; PLT: platelet; WBC: white blood cell.

Table 2. Response rates at week 27 and week 40 in different subgroups of aplastic anemia.

Response	Week 27				Week 40			
	Very severe AA N=4	Severe AA N=13	Non-severe transfusion-dependent N=2	*P*	Very severe AA, N=3	Severe AA N=9	Non-severe transfusion-dependent N=2	*P*
ORR, % (95% CI)	100 (51-100)	92.3 (66.7-98.6)	50 (9.5-90.5)	0.24	100 (51-100)	88.9 (56.5-98)	50 (9.5-90.5)	0.31
Trilineage response rate, % (95% CI)	25 (4.6-69.9)	53.8 (29.1-76.8)	50 (9.5-90.5)	0.77	50 (15-85)	55.6 (26.7-81.1)	0	0.50
CHR, % (95% CI)	0	23.1 (8.2-50.3)	0	0.67	0	33.3 (12.1-64.6)	0	0.36

AA: aplastic anemia; CHR: complete hematologic response; CI: Confidence Interval; N: number; ORR: overall response rate.

of dose optimization. The addition of eltrombopag to IST in untreated adults with severe AA has shown significant benefits, increasing the ORR from 40% with IST alone to 68% with combination therapy (pooled odds ratio: 3.2, 95% CI: 1.3-7.8).[9] Similarly, a cohort study involving Chinese children with SAA reported a remarkable ORR of 94.4% when eltrombopag was initiated on the first day of IST and continued for at least six months.[10] The efficacy of eltrombopag as an upfront treatment for severe AA has been further validated in systematic reviews and meta-analyses.[11,12] Despite these encouraging results, a subset of patients remains refractory to IST combined with eltrombopag or experiences disease relapse. Moreover, treatment with IST plus eltrombopag has demonstrated lower efficacy in children compared to adults.[2,13] High-dose romiplostim (20 mcg/kg/week) has emerged as an effective rescue therapy, inducing hematologic responses in up to 76% of patients refractory to eltrombopag.[14,15] Data on the use of romiplostim combined with IST as first-line treatment for pediatric AA remain limited. Dhingra *et al*.[5] studied 12 untreated AA patients aged 8-65 years treated with IST and romiplostim (up to 10 mcg/kg/week), reporting a hematologic response rate of 66.7% and a complete response rate of 25% at six months. While it is not clear how many children were enrolled, they treated their patients with lower doses of romiplostim (maximum 10 mcg/kg/week) and achieved a lower ORR at six months compared to our study (66.7% *vs*. 89.5%). Another study in USA evaluated romiplostim (median dose: 10 mcg/kg/week, range: 5-17.5 mcg/kg/week) with or without IST in 9 patients under 21 years with newly diagnosed or relapsed/refractory severe AA, demonstrating a CHR of 70.4% (95% CI: 20.2-92.6%) at 24 weeks.[6] However, their study population was heterogeneous, including both new and relapsed/refractory AA. While they included 9 patients with SAA, only 4 of them were treated with IST+romiplostim, which was much lower than our cohort. Furthermore, their definition of trilineage and complete hematologic response differed from ours.

Our study represents the first clinical trial in the pediatric population to evaluate the efficacy, safety, and tolerability of romiplostim as first-line therapy in IST-naïve AA patients. We observed a notable hematologic response at the 10-month follow-up and a significant reduction in transfusion requirements. Over 80% of transfusion-dependent patients achieved transfusion independence by week 40 of the study. Our study was unique due to the homogeneity of the study population and the dose of romiplostim, which was higher than in previous works. Only one similar work was conducted earlier,[6] but their patients were not homogeneous (AA treated with and without IST, and myelodysplastic syndromes [MDS]), and much smaller cohorts (only 4 children treated with romiplostim+IST).

Regarding safety, minor adverse effects such as myalgia, headache, and muscle spasms were reported, all of which were transient and did not necessitate dose reduction or discontinuation of romiplostim. Long-term concerns, including the risk of clonal evolution and bone marrow fibrosis, remain under investigation. While previous studies have reported karyotype abnormalities, such as monosomy 7, in adults treated with romiplostim, no cases of MDS, acute myeloid leukemia, or marrow fibrosis were observed.[3,7] Similarly, no cytogenetic abnormalities or bone marrow fibrosis were detected in our cohort at the end of the study.

The main limitation of our study was the lack of a control group for comparison. Given the rarity of AA in children, we could enroll the patients in a single-arm study, and the results were compared with historical data, which limited the generalizability of our findings. Future multicenter, randomized two-arm studies involving diverse ethnic populations and comparing the efficacy of IST with and without romiplostim may validate our results. Similarly, a head-to-head comparison of romiplostim with eltrombopag in treating pediatric AA may elucidate which treatment strategy is superior.

In conclusion, romiplostim, starting at 10 mcg/kg/week and titrated up to 20 mcg/kg/week, represents a promising addition to IST as a first-line treatment for children with severe AA. The drug is well tolerated, with an acceptable safety pro-

file, and significantly improves hematologic outcomes while reducing transfusion dependence. These findings underscore the potential of romiplostim as a valuable therapeutic option for pediatric AA. Larger, controlled studies are warranted to confirm these results and optimize treatment strategies.

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Contributions

MB generated the study concept, designed the study protocol, and edited the manuscript. AF collected the data and wrote the initial draft. ORZ and MSH participated in the treatment of patients. SHB helped in writing and editing the manuscript. All the authors read and approved the final manuscript.

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Data-sharing statement

The data and analysis will be shared upon appropriate request to the corresponding author.

References

1. Desmond R, Townsley DM, Dunbar C, Young NS. Eltrombopag in aplastic anemia. Semin Hematol. 2015;52(1):31-37.
2. Goronkova O, Novichkova G, Salimova T, et al. Efficacy of combined immunosuppression with or without eltrombopag in children with newly diagnosed aplastic anemia. Blood Adv. 2023;7(6):953-962.
3. Jang JH, Tomiyama Y, Miyazaki K, et al. Efficacy and safety of romiplostim in refractory aplastic anaemia: a phase II/III, multicentre, open-label study. Br J Haematol. 2021;192(1):190-199.
4. Yamazaki H, Lee JW, Jang JH, et al. P827: efficacy and safety of romiplostim added to immunosuppressive therapy as a first-line treatment in patients with aplastic anemia: a phase 2/3 clinical trial. Hemasphere. 2022;6(Suppl):721-722.
5. Dhingra G, Rajoreya A. A single-centre experience of first-line romiplostim and immunosuppressive therapy in patients with aplastic anemia. Cureus. 2023;15(4):e37682.
6. Sharathkumar A, Carr J, Claassen D, et al. Romiplostim for treatment of children and young adults with severe aplastic anemia and myelodysplastic syndrome. J Pediatr Hematol Oncol. 2024;46(5):252-261.
7. Mitani K, Lee JW, Jang JH, et al. Long-term efficacy and safety of romiplostim in refractory aplastic anemia: follow-up of a phase 2/3 study. Blood Adv. 2024;8(6):1415-1419.
8. Lee JW, Lee SE, Jung CW, et al. Romiplostim in patients with refractory aplastic anaemia previously treated with immunosuppressive therapy: a dose-finding and long-term treatment phase 2 trial. Lancet Haematol. 2019;6(11):e562-e572.
9. Peffault de Latour R, Kulasekararaj A, Iacobelli S, et al. Eltrombopag added to immunosuppression in severe aplastic anemia. N Engl J Med. 2022;386(1):11-23.
10. Fang M, Song H, Zhang J, Li S, Shen D, Tang Y. Efficacy and safety of immunosuppressive therapy with or without eltrombopag in pediatric patients with acquired aplastic anemia: a Chinese retrospective study. Pediatr Hematol Oncol. 2021;38(7):633-646.
11. Guo H, Liu C, Kang L, Liu C, Liu Y. Safety and efficacy of eltrombopag in patients with aplastic anemia: a systematic review and meta-analysis of randomized controlled trials. Hematology. 2024;29(1):2335419.
12. Zhang Y, Li J, Li X, et al. Efficacy and safety of immunosuppressive therapy combined with eltrombopag for severe aplastic anemia: a systematic review and meta-analysis. Syst Rev. 2024;13(1):101.
13. Groarke EM, Patel BA, Diamond C, et al. Outcomes in pediatric patients with severe aplastic anemia treated with standard immunosuppression and eltrombopag. Blood. 2019;134(Supplement_1):454.
14. Hosokawa K, Yamazaki H, Tanabe M, Imi T, Sugimori N, Nakao S. High-dose romiplostim accelerates hematologic recovery in patients with aplastic anemia refractory to eltrombopag. Leukemia. 2021;35(3):906-909.
15. Ise M, Iizuka H, Kamoda Y, Hirao M, Kida M, Usuki K. Romiplostim is effective for eltrombopag-refractory aplastic anemia: results of a retrospective study. Int J Hematol. 2020;112(6):787-794.