haematologica
Journal of the Ferrata Storti Foundation

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

by Mohammadreza Bordbar, Alireza Faghihi, Omid Reza Zekavat, Mahdi Shahriari and Shayan Bordbar

Received: April 18, 2025.
Accepted: July 14, 2025.

Citation: Mohammadreza Bordbar, Alireza Faghihi, Omid Reza Zekavat, Mahdi Shahriari and Shayan Bordbar. Safety and efficacy of romiplostim in children with acquired aplastic anemia who are naïve to immunosuppressive therapy.
Haematologica. 2025 July 24. doi: 10.3324/haematol.2025.288078 [Epub ahead of print]

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

Mohammadreza Bordbar[1*], Alireza Faghihi[2], Omid Reza Zekavat[1], Mahdi Shahriari[1], Shayan Bordbar[3]

1. **Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran**
2. **Pediatric Department, Shiraz Medical School, Shiraz University of Medical Sciences, Shiraz, Iran**
3. **Student Research Committee, Shiraz Medical School, Shiraz University of Medical Sciences, Shiraz, Iran**

***Correspondence:**

Mohammadreza Bordbar, MD, MPH

Professor of Pediatric Hematology and Oncology

Address: Hematology Research Center, Research Tower, Namazi Hospital, Zand Blv., Shiraz, Iran, Tel: +98 71 36281528

E-mail: mbordbar53@gmail.com

bordbarm@sums.ac.ir

Trial registration: Iranian Registry of Clinical Trials 'IRCT20221129056655N2'

Running head: Romiplostim in untreated childhood aplastic anemia

Contribution

M.B. generated the idea, designed the study protocol, and edited the manuscript; A.F. collected the data and wrote the initial draft; O.R.Z., M.SH. participated in the treatment of patients; SH.B. helped in writing and editing the manuscript; and all the authors read and approved the final manuscript.

Disclosure:

The authors declare that they have no competing financial interests.

Data-sharing statement:

The data and analysis will be shared upon logical request from the corresponding author.

Acknowledgments

We acknowledge the patients and their families for participating in this study. This paper was relevant to A Faghihi's thesis.

Funding

This study was supported by a research grant from Shiraz University of Medical Sciences, grant number 27317. It was also partly supported by the Amgen Company and its representative in Iran, Behestan Darou.

ORCID profiles

M.B., 0000-0002-8071-6425
A.F., 0009-0006-7400-9704
O.R.Z., 0000-0002-0008-3198
M.SH., 0000_0001_5104_9590
SH.B., 0009-0008-2413-7614

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 (IRCT20221129056655N2) 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 started on the first day of ATG infusion. Dose adjustments were based on platelet response and toxicity, increasing every 4 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 7 months (27 weeks), with a subset followed for an extended period of 10 months (40 weeks). Romiplostim was tapered and discontinued upon achieving trilineage hematopoiesis sustained for 8 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 7 months (27 weeks), with 15 patients were followed for an extended period of 10 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 (Figure S1). Significant improvements in hematologic parameters were observed during the 7-month follow-up (Figures 1A-1C). Among the 15 patients followed for 10 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% 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 (Hb <7 g/dL or platelets <10 × 10^9/L in stable patients) to minimize the risk of alloimmunization for potential 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 8 weeks. Six out of eight 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 (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 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 6 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 6 months compared to our study (66.7% vs. 89.5%). Another study in India evaluated romiplostim (median dose: 10 mcg/kg/week, range: 5-17.5 mcg/kg/week) with or without IST in nine 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 inhomogeneous (AA treated with and without IST, and 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 myelodysplastic syndrome, 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 profile, 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.

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.

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

	Baseline (n=19)	Week 27 (n=19)	Week 40 (n=15)	P1 (baseline and wk 27)	P2 (baseline and wk 40)	P3 (wk 27 and wk 40)
WBC ($\times 10^9$/L) Mean (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
ANC ($\times 10^9$/L) Mean (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
HB (g/dL) Mean (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
PLT ($\times 10^9$/L) Mean (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
Absolute reticulocyte count ($\times 10^9$/L) Mean [Min-Max]	24.73 [0.31-7.23]					

WBC: White blood cell; ANC: absolute neutrophil counts; HB: hemoglobin; PLT: platelet

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

	Week 27				Week 40			
	Very severe AA (n=4)	**Severe AA (n=13)**	**Non-severe transfusion-dependent (n=2)**	**P value**	**Very severe AA (n=3)**	**Severe AA (n=9)**	**Non-severe transfusion-dependent (n=2)**	**P value**
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; ORR: overall response rate; CI: confidence interval

Figure legends

Figure 1: Hematologic responses following treatment with romiplostim. A) Mean WBC and neutrophil changes; B) Mean hemoglobin changes; C) Mean platelet changes; D) Overall, trilineage, and complete hematologic response rates, and response in different hematologic parameters

ORR: overall response rate; CHR: complete hematologic response; WBC: white blood cells; ANC: absolute neutrophil count; HB: hemoglobin; PLT: platelet

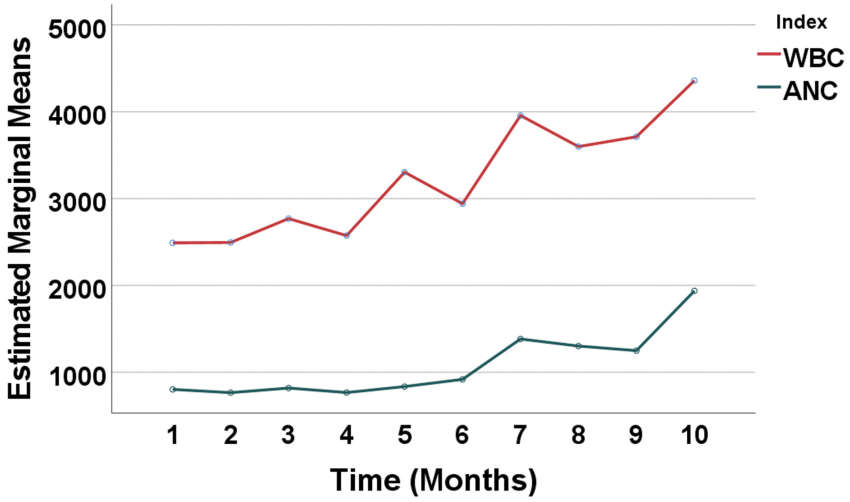


Figure 1A

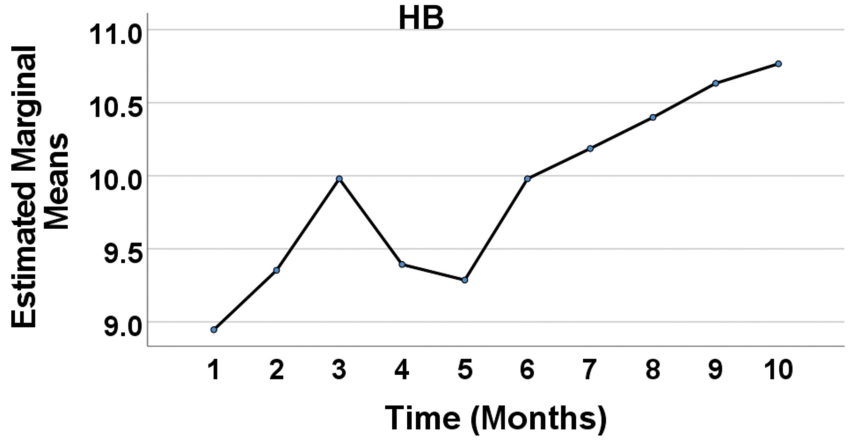


Figure 1B

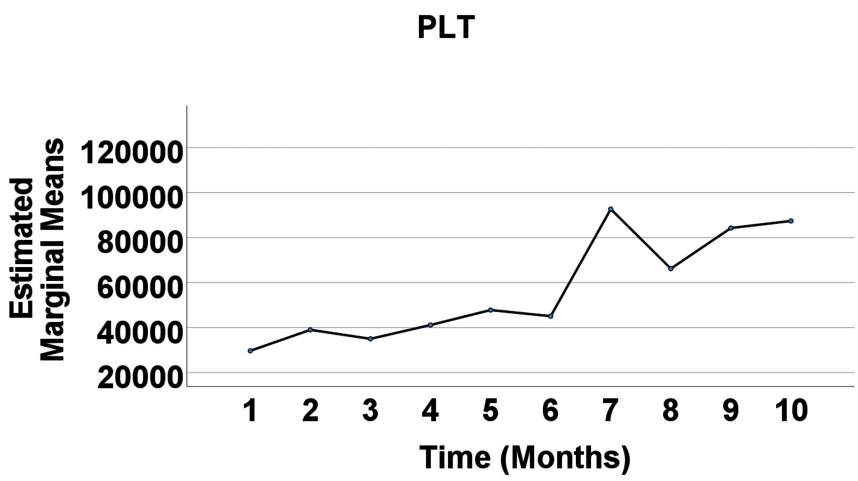


Figure 1C

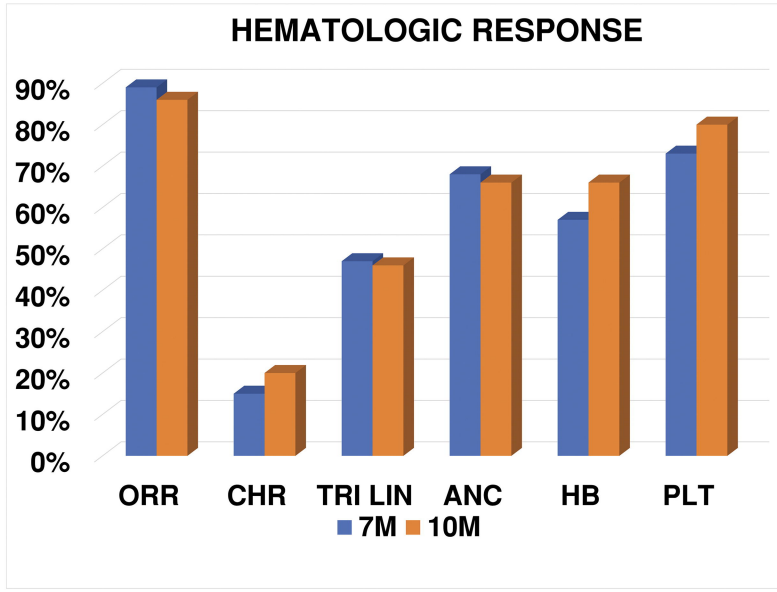


Figure 1D

Table S1- Definition of hematologic response

• **Platelet Response**: o Increase of ≥20 × 10^9/L above baseline; OR o Increase to ≥10 × 10^9/L with a ≥100% increase from baseline; AND o No platelet transfusions for 8 weeks in patients who had received transfusions in the 8 weeks prior to romiplostim initiation
• **Erythrocyte Response**: o Increase in hemoglobin to ≥9 g/dL without RBC transfusion in patients with pre-treatment hemoglobin <9 g/dL; OR o ≥50% reduction in cumulative RBC transfusion volume over 8 weeks in patients who had received transfusions in the 8 weeks prior to romiplostim initiation
• **Neutrophil Response**: o ≥100% increase in patients with baseline neutrophils <0.5 × 10^9/L; OR o Increase of ≥0.5 × 10^9/L above baseline in patients with baseline neutrophils of 0.5–1 × 10^9/L.
• **Trilineage Response**: o Achievement of concurrent platelet, erythrocyte, and neutrophil responses
• **Complete hematologic response (CHR)** o Platelet ≥150 × 10^9/L; AND o Hb ≥ 2 SD above the mean for age; AND o Neutrophil ≥1.5 × 10^9/L; AND o Transfusion independence in the past 8 weeks
• **Partial response (PR)**: Achievement of unilineage or bilineage hematologic response
• **Overall response (OR)**: The sum of responders with partial and trilineage responses

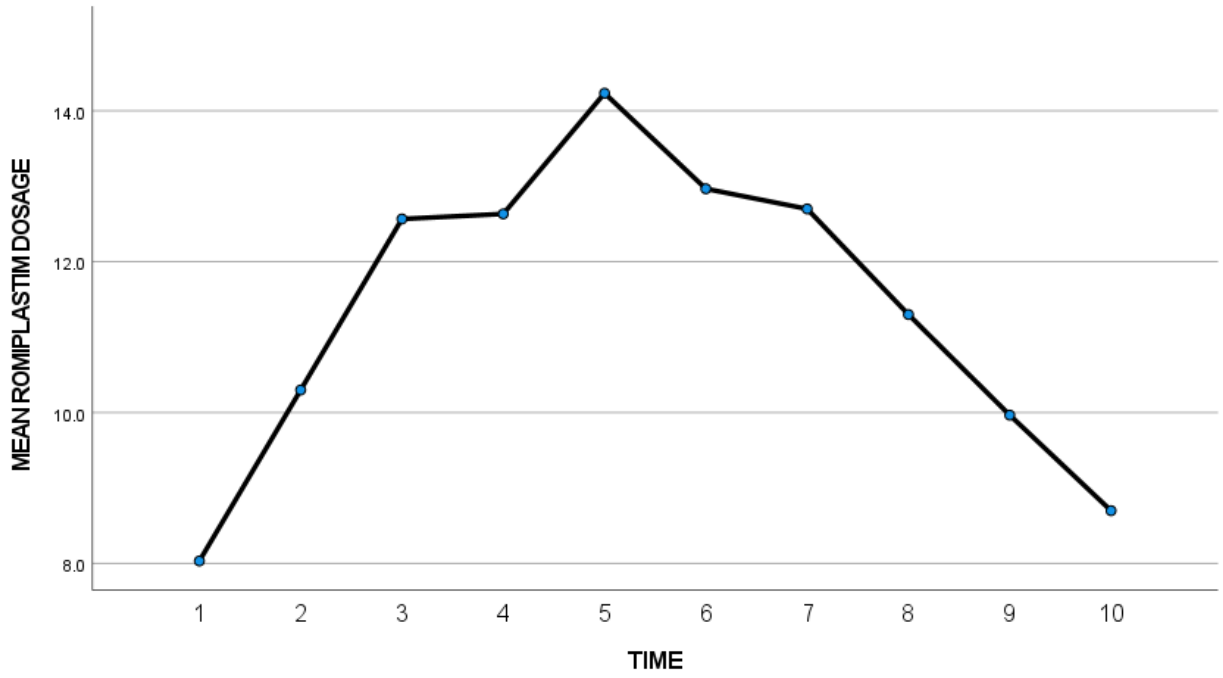
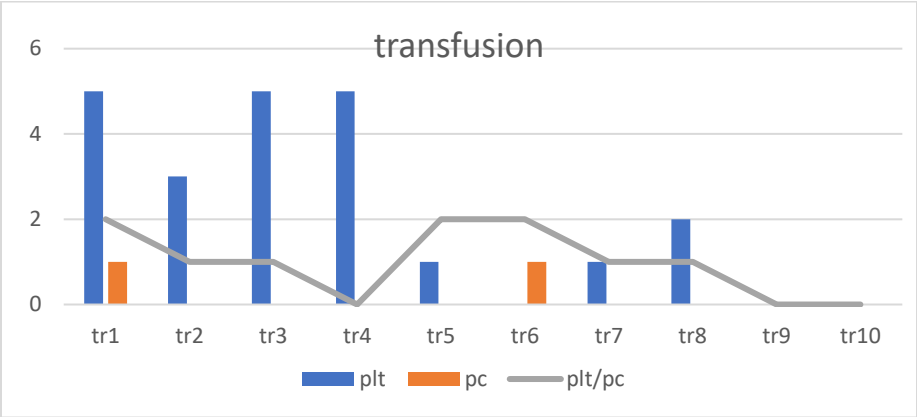


Figure S1: The trend of changes in romiplostim dosages during the 10-month follow-up



PLT: platelet; PC: packed red blood cells

Figure S2- Transfusion requirements in the 10 months' treatment with romiplostim