Higher doses of romiplostim than the maximum standard dose may be safe and effective in cases of inadequate response to the standard dose: case report

EDITED BY:

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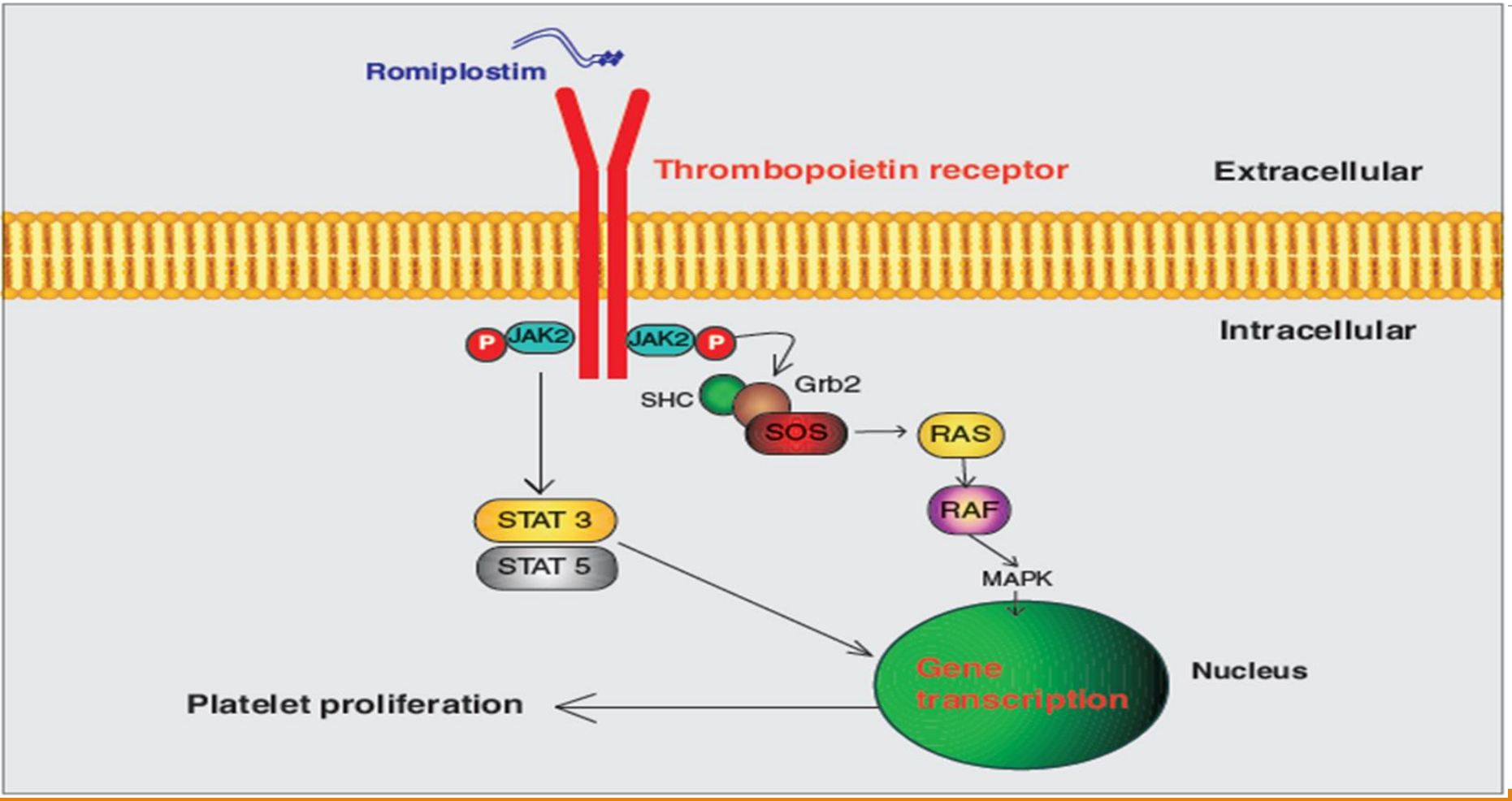
Introduction

Romiplostim is an Fc-peptide fusion protein (peptibody) that stimulates intracellular transcriptional pathways, which results in increased platelet production by binding to the TPO receptor.

Produced by recombinant DNA technology in Escherichia coli, romiplostim mimics human TPO.

Mechanism of action for romiplostim (Nplate)



When binding occurs to the TPO receptors, it promotes the growth of bone marrow megakaryocyte colony-forming cells, leading to increased platelet production via JAK2 and STAT5 kinase pathways.

Introduction

It stimulates the differentiation and proliferation of bone marrow cells responsible for producing platelets (megakaryocytes), thereby increasing platelet production and platelet counts (concentrations).

Dosage

After a single SQ injection with romiplostim (dose range, 1–10 mcg/kg) in patients with chronic ITP, the onset of peak response was reported to be 1.3 to 14.9 times greater than baseline platelet values over two to three weeks.

The time to peak concentration (Tmax) with romiplostim is approximately 7 to 50 hours (median, 14 hours for the post weekly (dose).

Approval

Overall Marketing Approval Date for Chronic ITP: 08/22/2008

Marketing Approval Date for Chronic ITP in children: 08/22/2015

Off-lable use:

- post-transplant thrombocytopenia,
- myelodysplastic syndrome (MDS)
- thrombocytopenia associated to lymphoproliferative diseases
- IST for Aplastic anemia
- Post-chemotherapy thrombocytopenia in solid tumors

Thrombotic/thromboembolic complications

deep vein thrombosis,

pulmonary embolism, and

myocardial infarction

observed with the use of romiplostim in the ITP population

The incidence of thrombotic/thromboembolic events observed in clinical trials was up to 6.0% (Adult group)

Caution

patients with known risk factors for thromboembolism including:

- inherited (e.g. Factor V Leiden) or
- acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome),
- advanced age,
- patients with prolonged periods of immobilization,
- malignancies,
- contraceptives and hormone replacement therapy,
- surgery/trauma,
- obesity and smoking

Table 2 Adverse Drug Reactions Identified with the Use of Romiplostim (Nplate) In Two Placebo-Controlled Studies

Preferred Term	Nplate (n = 84)	Placebo (n = 41)
Arthralgia	26%	20%
Dizziness	17%	0%
Insomnia	16%	7%
Myalgia	14%	2%
Pain in extremity	13%	5%
Abdominal pain	11%	0%
Shoulder pain	8%	0%
Dyspepsia	7%	0%
Paresthesia	6%	0%

Dose Adjustment

Platelet Count	Dose
Start	• 1 mcg/kg of actual body weight
Adjust • <50 × 10^9/L	• Adjust weekly dose by increments of 1 mcg/kg unit until platelet count reaches 50 x 10^9/L or greater. Do not exceed maximum weekly dose of 10 mcg/kg.
• >200 × 10^9/L for two consecutive weeks	• Reduce dose by 1 mcg/kg.
Discontinue • >400 × 10^9/L	• Do not administer. Continue to assess platelet count weekly. When platelet count has fallen below 200 x 10^9/L, resume once-weekly dose, reduced by 1 mcg/kg.

Initial Studies on drug dosage

The maximum dose of romiplostim allowed for cohorts 1 through 3 was 30 μg/kg, whereas in the final cohort, the dose was restricted to 10 μg/kg.

Phase III clinical trials

Starting dose:

- 1 μg/kg

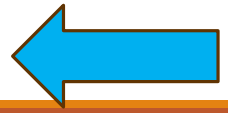
Subsequent dosing:

- 2 μg/kg every week if 10×10^9/L or less
- 2 μg/kg every 2 weeks if 11×10^9/L to 50×10^9/L

Maintenance dosing:

- Increase dose by 1 μg/kg every week if $<10\times10^9$/L
- Increase dose by 1 μg/kg after 2 weeks if 11×10^9/L to 50×10^9/L
- No dose adjustment if $50–200\times10^9$/L
- Reduce dose by 1 μg/kg after 2 consecutive weeks if 201×10^9/L–400×10^9/L
- Hold dose if $>400\times10^9$/L. Check platelet count weekly; resume at dose reduced by 1 μg/kg after platelet count $<200\times10^9$/L

Maximum allowed dose: 15 μg/kg



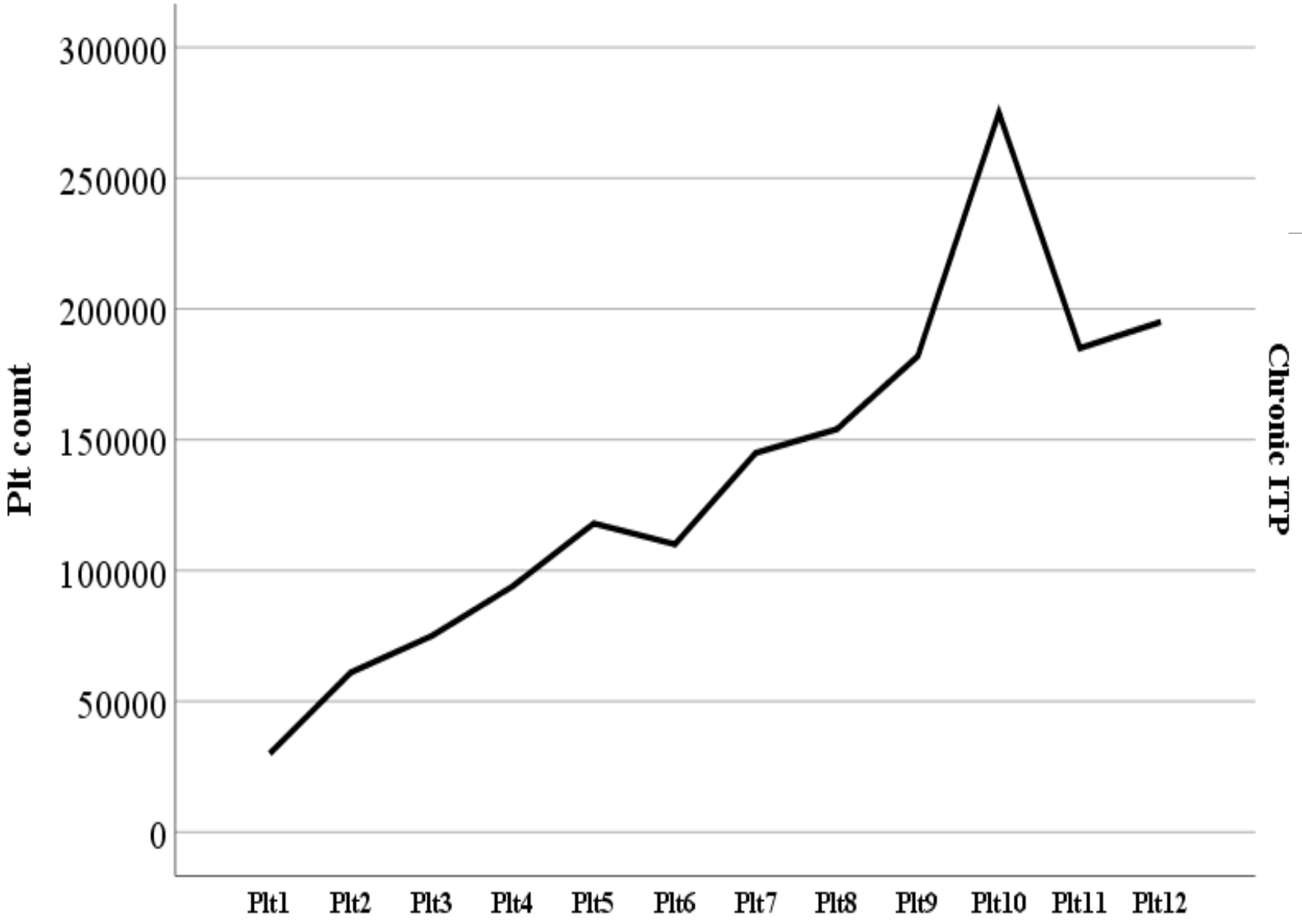
Challenging

Immune thrombocytopenia refractory to multiple thrombopoietin receptor agonists remains a challenging clinical problem.

Challenging

Drug	Dose	Response rate*
Low-dose prednisone	≤5 mg orally once per day	<10%
Rituximab	375 mg/m^2 IV once per week × 4 (lower doses may be effective)	60% overall, 40% complete, 20%-25% at 5 y
Romiplostim	1-10 μg/kg SC once per week	80% overall, 40%-50% persistent
Eltrombopag	25-75 mg orally once per day	80% overall, 40%-50% persistent

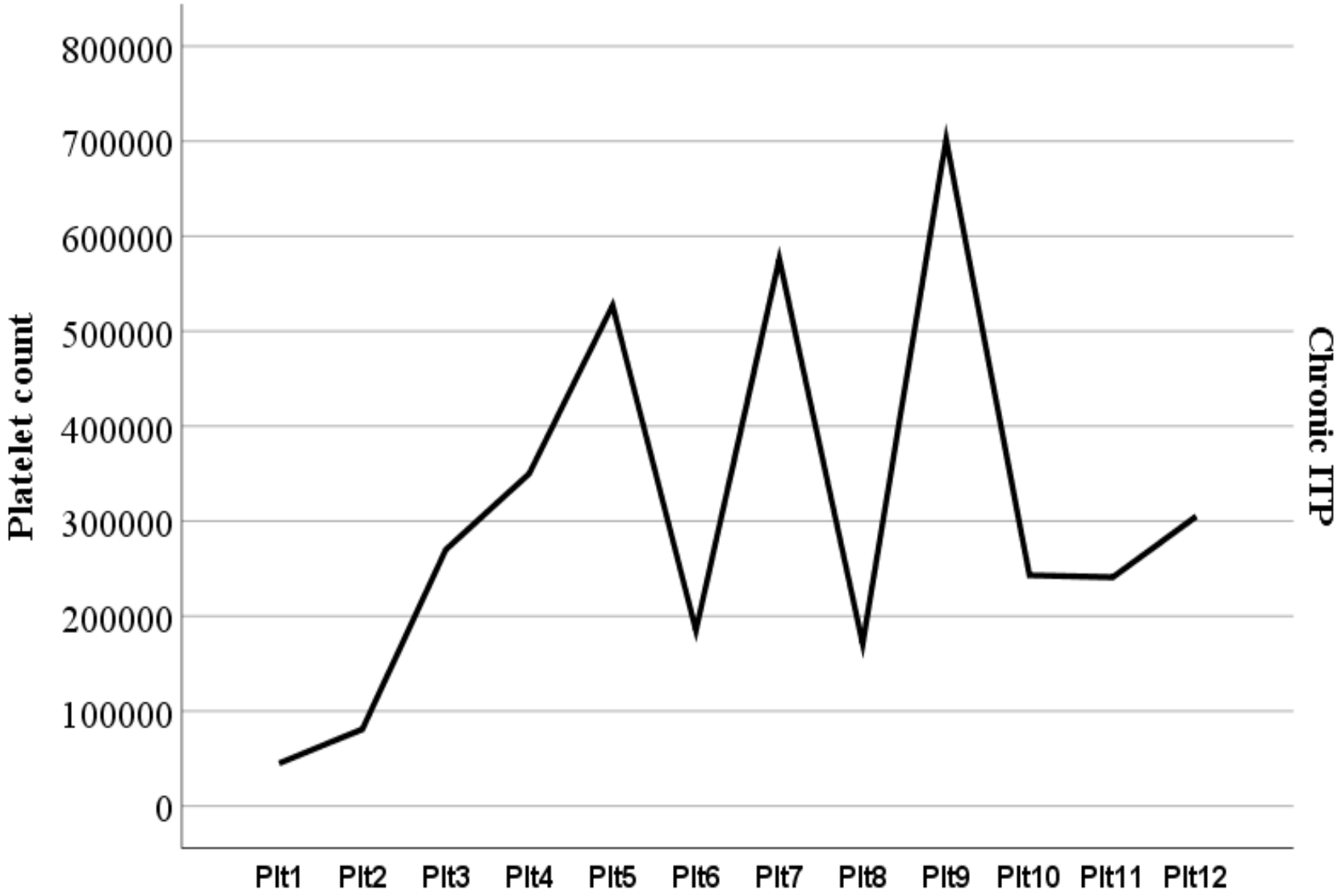
Case Presentation



Chronic ITP

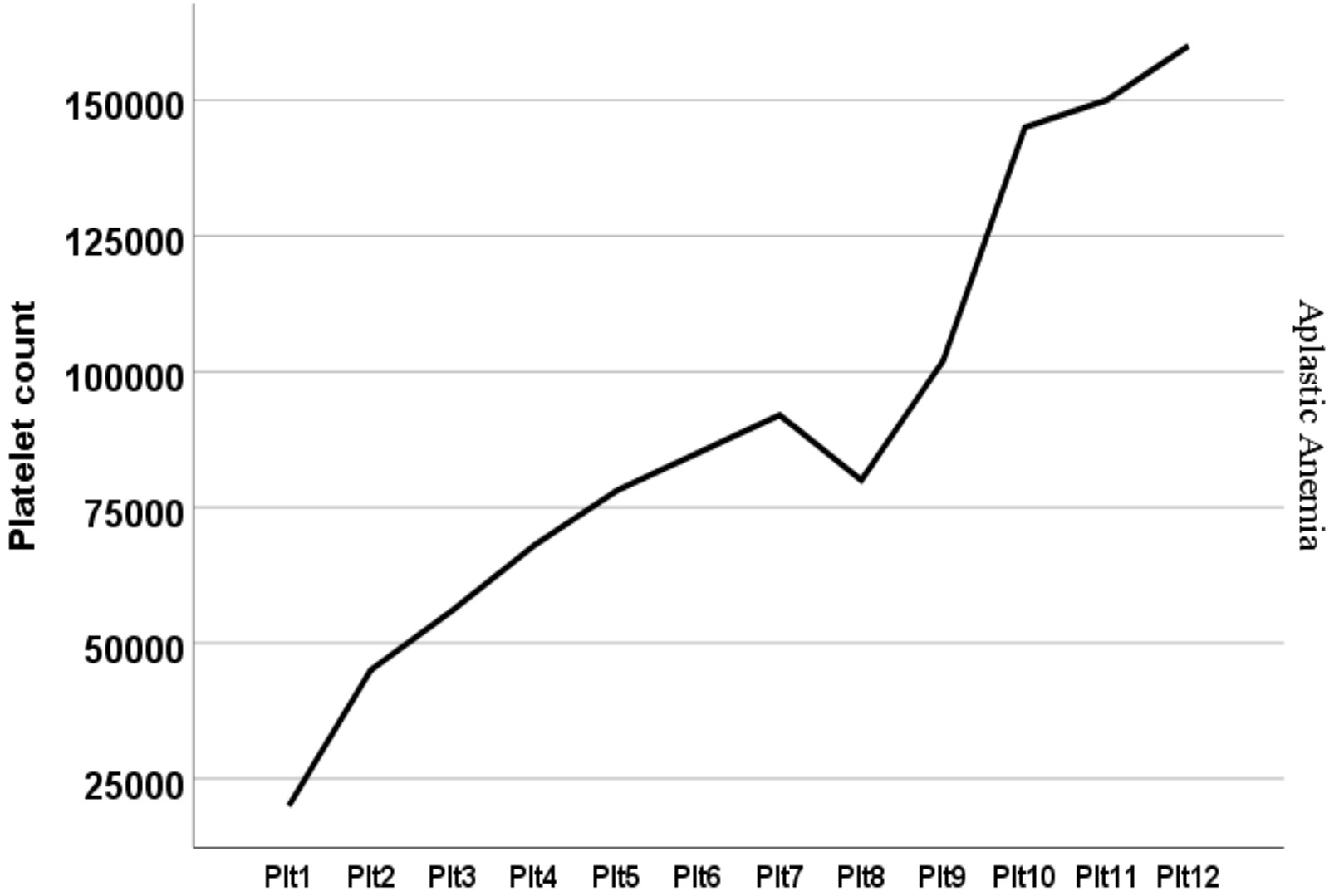
- 10-yr old boy
- Chronic ITP
- Without any underlying disorders
- Maximum Plt count with 10 µg/kg Nplate was 45000

Chronic ITP



- 4-yr old boy
- Chronic ITP
- Since 2-yr of age
- Without any underlying disorders
- Maximum Plt count with 10 µg/kg Nplate was 55000

Severe Aplastic Anemia



5-yr old boy

8 months after IST

Maximum Plt count after 10 µg/kg Nplate was 30000

Literature review

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

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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]

Study design

single-arm study

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patients aged <18 years with untreated severe/very severe AA or transfusion-dependent non-severe AA.

subcutaneous romiplostim (10 mcg/kg/week initially for 4 weeks, titrated to 20 mcg/kg/week, in increments of 5mcg/kg/week from week 5-27) alongside IST (horse ATG 40 mg/kg/day × 4 days and cyclosporine 10 mg/kg/day).

Study design

Romiplostim started on the 1st 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.

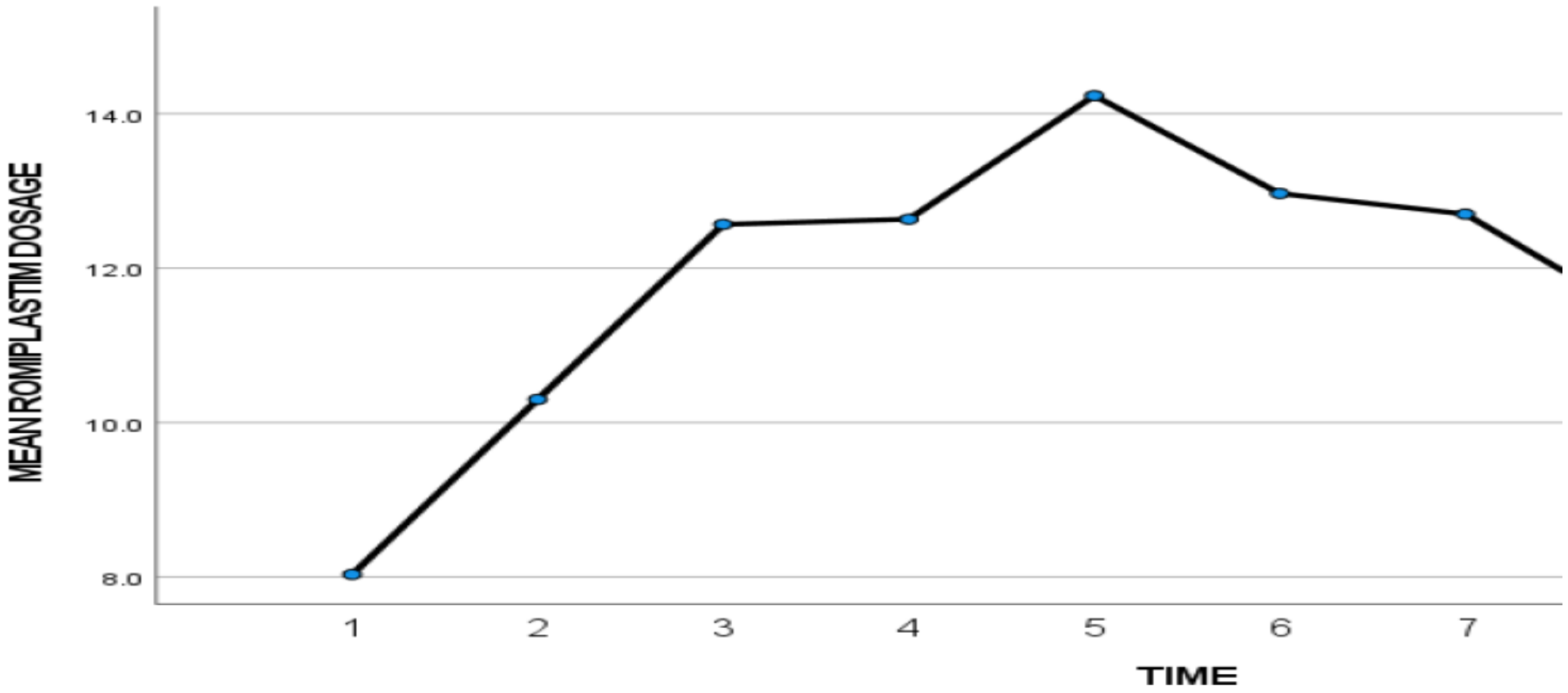
followed monthly for 7 months (27 weeks),

tapered and discontinued upon achieving trilineage hematopoiesis sustained for 8 weeks at the same romiplostim dose without transfusion.

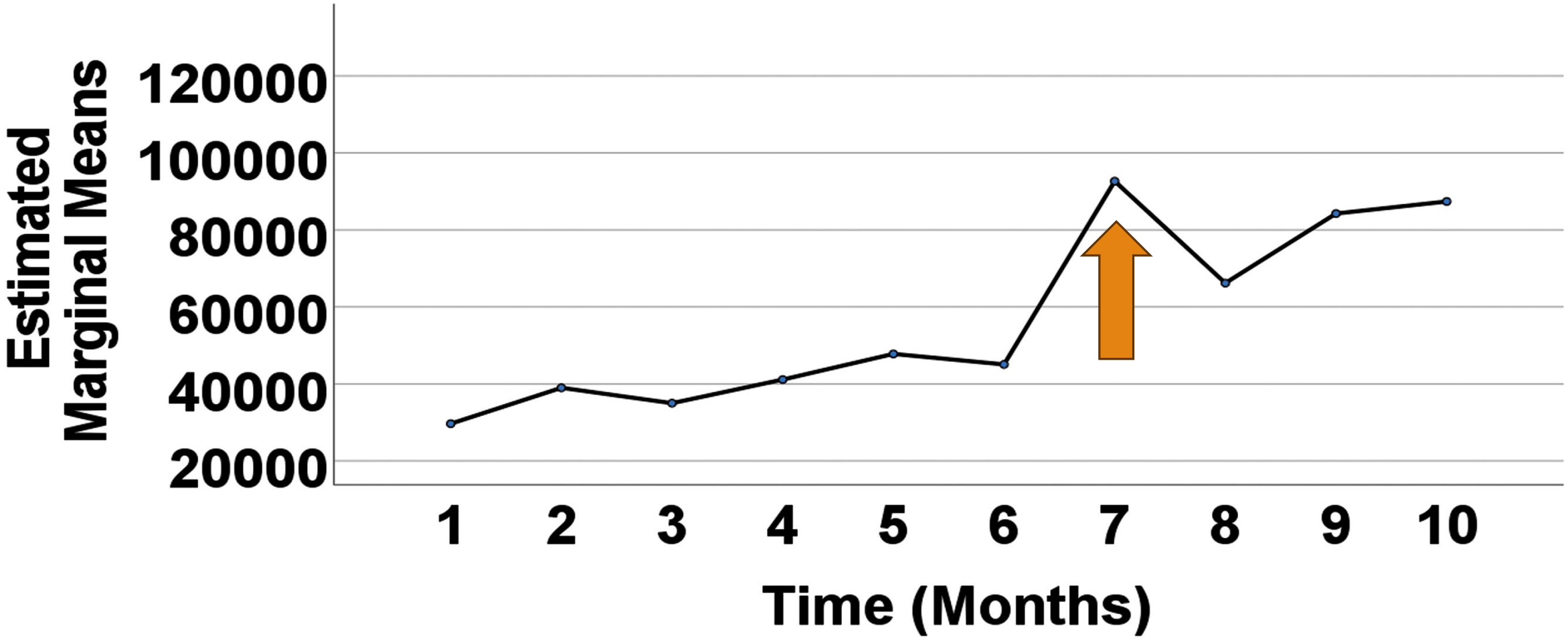
Results

17 patients [12 males (63.2%), median age 6 years (range: 3–15 years), with severe/very severe AA] who were followed for 7 months (27 weeks), The median romiplostim dosage was 12 mcg/kg/week (range: 8–15 mcg/kg/week)

The trend of changes in romiplostim dosages during the 7-month follow-up



PLT


Estimated Marginal Means
120000
100000
80000
60000
40000
20000
1
2
3
4
5
6
7
8
9
10
Time (Months)

Leukemia
https://doi.org/10.1038/s41375-020-0950-6

LETTER

Stem cell biology

High-dose romiplostim accelerates hematologic recovery in patients with aplastic anemia refractory to eltrombopag

Kohei Hosokawa[1] · Hirohito Yamazaki[2] · Mikoto Tanabe[1] · Tatsuya Imi[1] · Naomi Sugimori[1] · Shinji Nakao[1]

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To the Editor:

Patients with acquired aplastic anemia (AA) refractory to eltrombopag (EPAG) have been reported to respond poorly to another thrombopoietin receptor agonist (TPO-RA), romiplostim (ROMI), in doses of up to 10 μg/kg per week. We analyzed the effectiveness of 20 μg/kg ROMI in 21 patients with EPAG-refractory AA. Sixteen of 21 (76%) achieved a hematologic response in at least one lineage at 3 months. Five of ten (50%) patients became

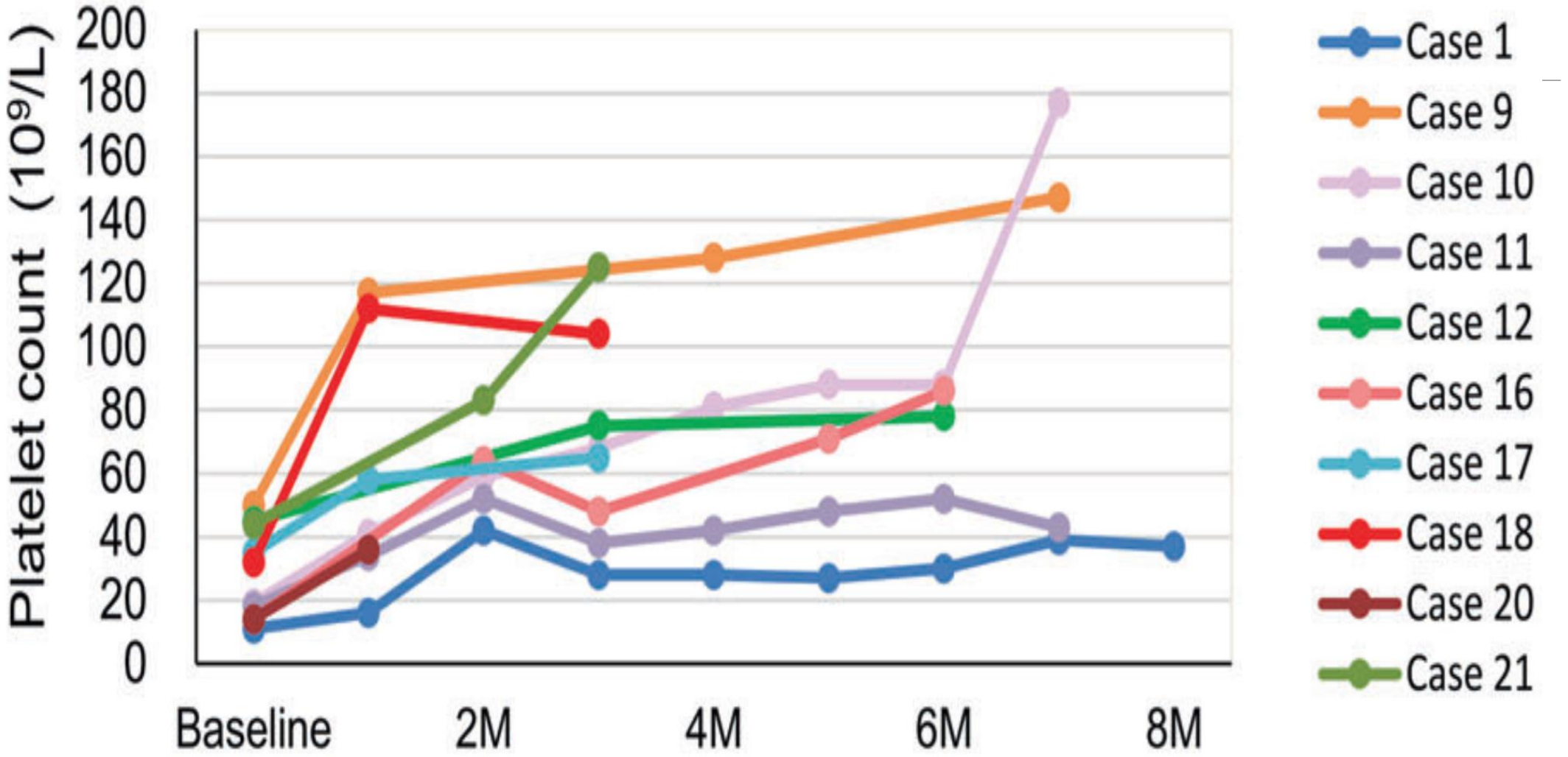
EPAG, a TPO-RA, has been shown to induce hematologic recovery in about 50% of patients with AA refractory to IST [3–6]. Moreover, EPAG was reported to increase response rates when added to ATG/CsA in treatment-naive SAA patients compared with a historical cohort [7]. Although EPAG has changed the paradigm of AA treatment, novel therapies are still needed to rescue EPAG-refractory patients. A recent clinical trial showed that another TPO-RA, ROMI, was effective in ~80% of EPAG-naïve patients with refractory SAA or non-severe

Trials design

ROMI was initially administered at 10 μg/kg,

- and continued at the same dose (n = 1)
- or increased up to 15 (n = 2)
- or 20 (n = 18) μg/kg weekly for 12–40 (median: 24) weeks in the 21 pt who:
  - showed no response (defined as primary refractory, n = 10) or
  - only a minimal response to EPAG (defined as a reduction of red blood cell transfusions, improvement of blood counts, and not meeting the response criteria by 6 months of EPAG treatment, n = 11).

All 21 patients tolerated ROMI and showed no severe treatment-related adverse events that necessitated ROMI discontinuation.



International Journal of Hematology
https://doi.org/10.1007/s12185-020-02971-1

ORIGINAL ARTICLE

Romiplostim is effective for eltrombopag-refractory aplastic anemia: results of a retrospective study

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Received: 11 May 2020 / Revised: 29 July 2020 / Accepted: 7 August 2020

Abstract

Eltrombopag (EPAG) and romiplostim (ROM), thrombopoietin receptor-agonists with demonstrated efficacy against aplastic anemia (AA) in prospective controlled studies, were authorized in Japan for use in adults with aplastic anemia in 2017 and 2019, respectively. So far, no data are available on the potential contribution of switching from ROM to EPAG or vice versa in terms of efficacy or tolerance. Efficacies and tolerance profiles of ten patients, who failed to respond to the maximum dose of EPAG and then switched to ROM, were evaluated. All ten patients received a maximum dose of ROM (20 µg/kg/week). At a median follow-up of twelve months, seven of ten patients (70%) had achieved either neutrophil, erythroid, or platelet response, including one complete response. No patients showed platelet count fluctuations that were reported during ROM treatment for immune thrombocytopenia. In univariate analysis of the relationship between efficacy and demographics, the

10 patient

20 µg/kg/wkly

Age range: 29-84 yr

Without any side effects

50% response rate

Observational Study > J Pediatr Hematol Oncol. 2024 Jul 1;46(5):252-261.
doi: 10.1097/MPH.0000000000002891. Epub 2024 May 24.

Romiplostim for Treatment of Children and Young Adults With Severe Aplastic Anemia and Myelodysplastic Syndrome

Anjali Sharathkumar [1 2], Jamie Carr [3], David Claassen [1], Sergei Syrbu [4], Sharathkumar Bhagavathi [4], Ahmad Al-Huniti [5], Arunkumar Modi [6], Melissa Bates [2 7 8], Sarah L Mott [2]

Affiliations + expand

PMID: 38787686 DOI: 10.1097/MPH.0000000000002891

Abstract

Thrombopoietin receptor agonists (TPO-RAs) induce trilineage hematopoiesis under conditions with acquired hematopoietic failure. We evaluated safety, tolerability, and preliminary efficacy of a TPO-RA, romiplostim (Nplate), with or without standard-of-care immunosuppressive therapy (±IST) for children (ages < 21 y) with newly diagnosed and relapsed/refractory severe aplastic anemia (SAA) and myelodysplastic syndrome (MDS). Data were collected from an observational study and a single arm

children (ages < 21 y) with newly diagnosed and relapsed/refractory SAA and MDS.

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single arm interventional pilot study. maximum, 20 µg/kg/dose

Median romiplostim dose was 10 µg/kg/week (range: 5 to 17.5 µg/kg/week).

76% CHR

3/21 Pt AEs (Grade 1-3)

Annals of Hematology (2025) 104:3863–3867
https://doi.org/10.1007/s00277-025-06448-1

CASE REPORT

High-dose romiplostim for donor-type aplasia

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Received: 5 August 2024 / Accepted: 31 May 2025 / Published online: 12 June 2025

Abstract

Donor-type aplasia (DTA) is a severe complication of allogeneic hematopoietic stem cell transplantation (allo-HSCT), characterized by bone marrow hypoplasia despite full chimerism. This report highlights the successful use of romiplostim (ROMI) for treating DTA in three patients with acquired aplastic anemia (AA), including two who were unresponsive to eltrombopag (EPAG). Case 1: A 21-year-old female with non-severe AA, treated with cyclosporine (CsA), rabbit anti-thymocyte globulin, and EPAG, showed no improvement. After undergoing bone marrow transplantation (BMT) from an HLA-matched sibling, she continued to experience pancytopenia. Switching from EPAG to ROMI 16 months after BMT led to transfusion independence after 7 weeks and normalized blood counts by 17 months. Case 2: A 35-year-old male with moderate AA, initially treated with CsA and ROMI, switched to EPAG before BMT from an HLA-matched sibling

DTA a severe complication of ALLO-HSCT

3 pt with SAAA with persistent thrombocytopenia after Allo-HSCT

Case 1: 15 µg/kg/wk

Case 2 & 3: 20 µg/kg/wk

all three DTA cases achieved trilineage complete responses without any serious adverse events.

Conclusion

It appears that higher dose than maximum recommended dose of Romiplastim (15-20 µg/kg/wk) may be safe an effective.

However, this result need to confirm in a large trial study, both in terms of impact and cost-effectiveness and short-term and long-term side effects.

THANK YOU FOR YOUR ATTENTION