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Romiplostim for aplastic anemia: beyond an eltrombopag alternative

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The combination of anti-thymocyte globulin (ATG), cyclosporine (CsA), and eltrombopag (EPAG) is widely regarded as the standard first-line therapy for patients with severe aplastic anemia (SAA) who are ineligible for allogeneic hematopoietic stem cell transplantation from an HLA-matched sibling donor[1]. In adult patients, the addition of EPAG has been shown to increase both the response rate at 6 months to ATG plus CsA and the failure-free survival rate at 2 years by 20–30%. However, this benefit has not been consistently observed in pediatric patients, highlighting an ongoing unmet need for children with SAA who lack a matched donor[2, 3].

Romiplostim (ROMI), a thrombopoietin receptor agonist (TPO-RA), has primarily been used in the treatment of immune thrombocytopenia (ITP), particularly in patients refractory to EPAG. Although some patients with EPAG-refractory ITP respond to ROMI, the thrombopoietic potential of the two TPO-RAs is generally considered comparable. Since the initial report from the National Institutes of Health group in the United States demonstrating the efficacy of EPAG in SAA patients refractory to immunosuppressive therapy (IST)[4], the therapeutic efficacy of ROMI in this context has been explored.

An initial French study using a ROMI dose of up to 10 μg/kg per week showed a limited efficacy[5]. In contrast, a phase II/III trial conducted in Japan and Korea used a higher dose (20 μg/kg/week) in IST-refractory patients and demonstrated a response rate

of 84% at week 27 in at least one hematopoietic lineage[6]. Subsequently, the efficacy of ROMI in patients refractory to the maximum dose of EPAG (100 mg/day) was evaluated in Japan and China. Table 1 summarizes four studies that reported similar response rates of approximately 70%, suggesting that ROMI at 20 μg/kg/week may exert a more potent hematopoietic effect than EPAG at 100 mg/day, which is considered equivalent to 200 mg/day, in Caucasian populations.

Given these encouraging results, pediatric hematologists have begun to explore the use of ROMI in treatment-naïve pediatric patients with SAA. In this issue of *Haematologica*, Bordbar et al. reported remarkably high overall response rates (ORRs) of 89.5% at week 27 and 86.7% at week 40, with minimal toxicities, in 19 pediatric patients with SAA treated with ATG, CsA, and ROMI (median ROMI dose: 12 μg/kg/week)[7]. These results are notably higher than the previously reported 6-months ORRs in the 60% range among pediatric patients treated with ATG, CsA, and EPAG at 6 months[2, 3], and even surpass the 68% ORR observed in adult patients treated with the same regimen[1]. Supporting evidence comes from a recent study conducted in Japan, Korea, and Taiwan, which reported an ORR of 87% at week 27 in 17 patients (12 with SAA and 5 with non-severe AA) treated with ATG, CsA, and ROMI, despite the use of rabbit-derived ATG[8]. Although a direct comparison of ROMI and EPAG in SAA is needed to determine

their superiority, these findings suggest that ROMI (20 μg/kg/week) may more effectively augment the response to ATG and CsA than EPAG (100 mg/day) in patients with SAA.

EPAG, a small-molecule TPO mimetic, stimulates hematopoietic stem cell (HSC) proliferation by binding to the transmembrane domain of the TPO receptor and entering the cells independently of the receptor. In contrast, ROMI is a fusion protein composed of an IgG Fc fragment and a peptide that targets the extracellular domain of TPO receptor, exerting its effect exclusively via receptor binding. The thrombopoietic effect of ROMI at a dose of 10 μg/kg/week is roughly comparable to that of EPAG at 50 mg/day in Japanese patients with ITP. Why, then, does ROMI at 20 μg/kg/week appear more effective than EPAG at 100 mg/day in patients with AA?

One plausible explanation may lie in the pharmacokinetics. Subcutaneously administered ROMI reaches the bone marrow without degradation by digestive enzymes, and is thought to persist at a relatively high concentration in the bone marrow microenvironment. Conversely, the oral formulation of EPAG is more susceptible to digestive and dietary effects. Additionally, EPAG may have a shorter half-life in children owing to increased metabolic clearance, resulting in lower bone marrow drug levels. It is also possible that ROMI stimulates primitive HSCs more effectively by inducing molecular mechanisms that involve RHOA signaling[9].

The precise mechanism by which TPO-RAs enhance ORRs in SAA remains unclear. If their benefit is derived solely from stimulating residual healthy HSCs, the hematologic response would not be expected to persist after discontinuation of the TPO-RA, especially given that ATG plus CsA is not fully immunoablative and that the T-cell–mediated attack on HSCs likely persists in a substantial proportion of patients (Figure 1A). However, in clinical practice, hematologic responses are often durable, lasting many years, or even lifelong, without continued CsA maintenance.

Recent studies have revealed that HSCs lacking the expression of HLA class I due to chromosome 6p loss of heterozygosity or inactivating mutations in HLA genes are detectable in nearly 50% of patients with AA at the time of their diagnosis[10]. These immune-evasive HSCs can escape T-cell–mediated destruction, but they initially fail to support hematopoiesis unless stimulated by agents such as TPO-RAs. During this delay, patients are at risk of life-threatening infections following ATG therapy. The concomitant use of TPO-RA may promote hematologic recovery by supporting the proliferation of these immune-escape HSCs (Figure 1B). ROMI may offer a unique advantage over EPAG in facilitating escape hematopoiesis when used in combination with ATG and CsA.

References

1. 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.

2. Groarke EM, Patel BA, Gutierrez-Rodrigues F, et al. Eltrombopag added to immunosuppression for children with treatment-naive severe aplastic anaemia. Br J Haematol. 2021;192(3):605-614.

3. 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.

4. Olnes MJ, Scheinberg P, Calvo KR, et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. N Engl J Med. 2012;367(1):11-19.

5. Zhao LP, Sicre De Fontbrune F, Contejean A, et al. Nationwide survey in France on the use of romiplostim in patients with refractory severe aplastic anemia. Bone Marrow Transplant. 2019;54(7):1161-1163.

6. 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.

7. Bordbar M, Faghihi A, Zekavat OR, Shahriari M, Bordbar S. Safety and efficacy of romiplostim in children with acquired aplastic anemia who are naive to immunosuppressive therapy. Haematologica. xxx

8. Lee JW, Jang JH, Yamazaki H, et al. Addition of romiplostim to immunosuppressive therapy as first-line treatment for patients with aplastic anemia. Blood Adv. 2025 Aug 4. [Epub ahead of print]

9. Tezuka Y, Onoda N, Morishima T, et al. Expansion effect of romiplostim on hematopoietic stem and progenitor cells versus thrombopoietin and eltrombopag. Int J Hematol. 2024;120(5):575-586.

10. Zaimoku Y, Hosomichi K, Tsuji N, et al. HLA class I allele-deficient clones regenerate in immune aplastic anemia without anti-thymocyte globulin. Blood. 2024;(Supplement 1):1307.

Table 1. Efficacy of Romiplostim in Patients Refractory to Eltrombopag

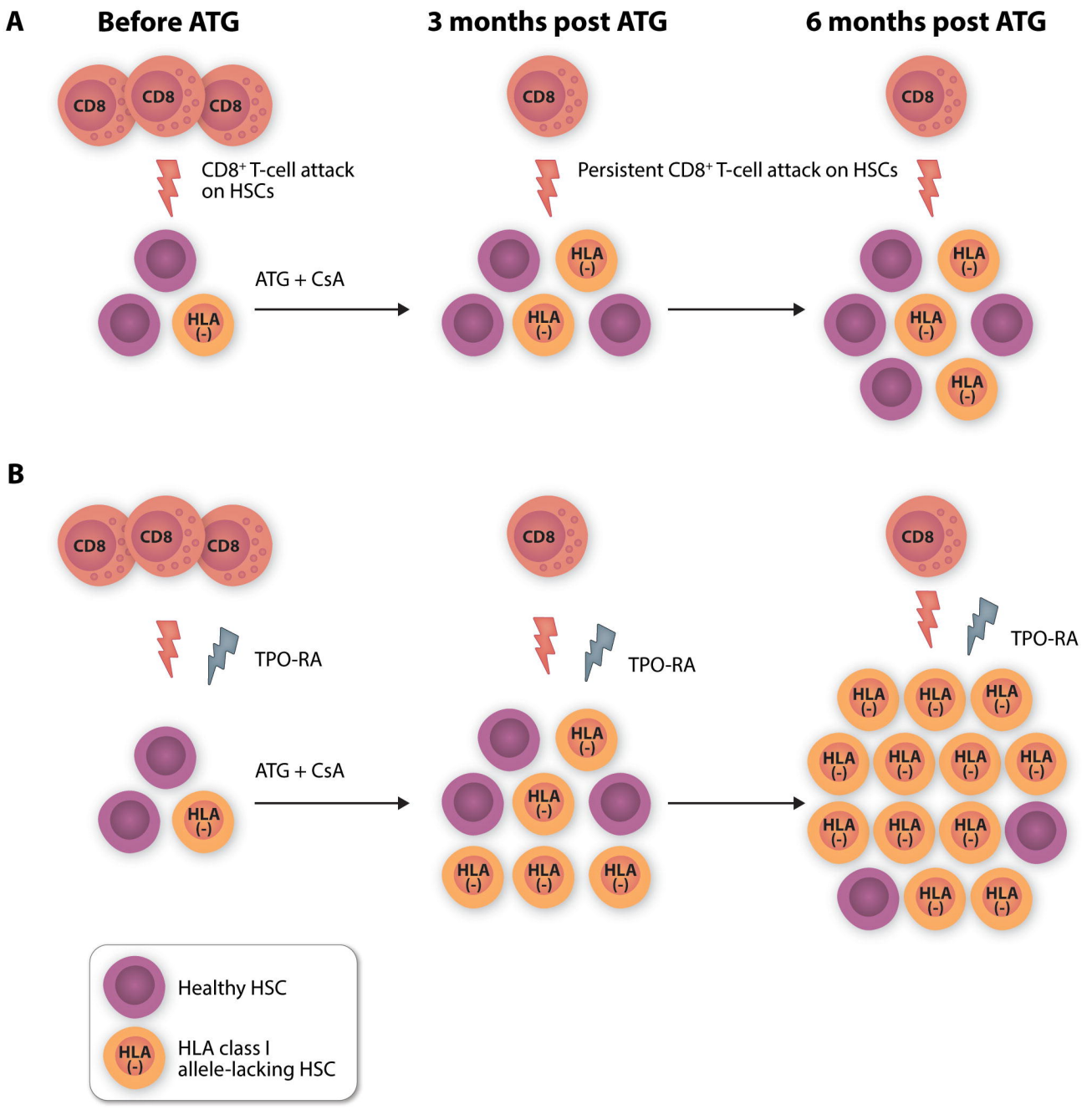
Study	No. of Patients (No. with SAA)	Duration of Prior EPAG Treatment (months, median [range])	Response Rate Overall (in SAA)	Reference
1	10 (2)	22 (3–26)	70% (50%)	Ise et al. Int J Hematol. 2020;112:787–794.
2	21 (11)	20 (2–56)	76% (50%)	Hosokawa et al. Leukemia. 2021;35:906–909.
3	7 (7)	8 (3–22)	71% (71%)	Sato et al. Rinsho Ketsueki. 2025;66:92–99.
4	7 (2)	6 (3–15)	72.8% (N/A)	Lin X et al. Ann Med. 2025;57:2514781.

Abbreviations: SAA, severe aplastic anemia; EPAG, eltrombopag; N/A, not available.

Figure legend

Figure 1. Proposed Mechanism of TPO-RA-Mediated Enhancement of Response to ATG plus CsA in severe aplastic anemia

(A) In patients treated with ATG + CsA alone, while some HLA class I allele-lacking (HLA[-]) HSCs evade immune attack and survive, their expansion is limited, resulting in incomplete hematopoietic recovery. **(B)** In patients treated with thrombopoietin-receptor agonist (TPO-RA) in addition to immunosuppression, HLA(−) HSCs not only escape immune attack but also undergo marked expansion, leading to improved hematopoiesis. Abbreviations: ATG, anti-thymocyte globulin; CsA, cyclosporine; TPO-RA, thrombopoietin receptor agonist; HSC, hematopoietic stem cell.


A
Before ATG
3 months post ATG
6 months post ATG
CD8
CD8
CD8
CD8+ T-cell attack on HSCs
Persistent CD8+ T-cell attack on HSCs
ATG + CsA
HLA (-)
B
TPO-RA
ATG + CsA
Healthy HSC
HLA class I allele-lacking HSC