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by Paul Saultier and Alessandro Pecci

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Paul Saultier¹ and Alessandro Pecci²

¹Aix Marseille Univ, APMH, INSERM, INRAe, C2VN, La Timone Children's Hospital, Department of pediatric hematology, immunology and oncology, Marseille, France

²Dipartimento Medico, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy; Dipartimento di Medicina Interna, Università di Pavia, Pavia, Italy.

Corresponding Author: Paul Saultier, Department of Pediatric Hematology and Oncology, La Timone Children's Hospital, APMH and Aix Marseille Univ, 264 rue Saint-Pierre, 13385 Marseille, France; E-mail: paul.saultier@gmail.com; phone: +33491386778; fax: +33491384989.

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To the Editor,

We read with great interest the report by Jian et al. describing sustained platelet recovery with avatrombopag in a child with congenital amegakaryocytic thrombocytopenia (CAMT) caused by a homozygous *THPO* c.355C>T (p.R119C) variant.¹ The observation of a durable hematological response to avatrombopag is clinically relevant and expands the limited experience with thrombopoietin receptor agonists (TPO-RA) in this ultra-rare disorder. However, we believe that the role attributed to allogeneic hematopoietic stem cell transplantation (allo-HSCT) deserves clarification, as the current presentation may suggest that allo-HSCT represents an appropriate component of the therapeutic strategy for *THPO*-mutated CAMT.

The molecular basis of CAMT is heterogeneous: in particular, distinction between *MPL*- and *THPO*-related disease is fundamental to therapeutic decisions. Germline biallelic *MPL* variants cause a hematopoietic cell-intrinsic defect: hematopoietic stem and progenitor cells cannot adequately respond to thrombopoietin. Allo-HSCT therefore replaces the defective hematopoietic compartment and remains the established curative treatment for CAMT-*MPL*.^{2,3} The favorable transplantation outcomes recently reported by an EBMT study should primarily be interpreted within this context.⁴ Indeed, current transplant recommendations describe CAMT essentially as an *MPL*-related disorder when defining indications for transplantation.⁵

The pathophysiology of *THPO* deficiency is fundamentally different. Thrombopoietin is produced predominantly by the liver, and biallelic loss-of-function *THPO* variants therefore cause a hematopoietic cell-extrinsic defect. Replacing hematopoietic stem cells cannot correct defective thrombopoietin production by recipient hepatocytes. Seo et al. clearly demonstrated this principle in five patients with biallelic *THPO* variants and bone marrow failure: four individuals underwent HSCT and experienced persistent severe cytopenias/poor graft function despite transplantation, whereas TPO-RA treatment improved trilineage hematopoiesis in the surviving patients.⁶ These findings established the importance of identifying *THPO* deficiency before referring CAMT patients for transplantation.

This issue is particularly relevant to the patient reported by Jian et al., because the same homozygous *THPO* p.R119C variant had already been characterized by Pecci et al. in three children with CAMT.⁷ Functional experiments demonstrated impaired *THPO* secretion and reduced *MPL* activation. Importantly, romiplostim induced sustained trilineage hematological responses, resolution of bleeding and infectious manifestations, and transfusion independence. The authors specifically emphasized that recognition of *THPO*-related CAMT is essential to provide TPO-RA therapy and avoid unnecessary HSCT.⁷

In the present patient, the homozygous p.R119C variant was identified approximately two years before allo-HSCT. The indication for transplantation is justified by Jian et al. by the development of “progressive bone marrow failure”. However, progression from thrombocytopenia to multilineage cytopenia and marrow hypoplasia is itself part of the phenotype of biallelic *THPO* deficiency and does not indicate the emergence of a hematopoietic cell-intrinsic disorder that would be corrected by HSCT.^{6,7} We therefore believe that the rationale for performing allo-HSCT despite the established molecular diagnosis deserves further discussion.

Interestingly, the post-transplant course may be consistent with the expected pathophysiology. Despite rapid and sustained complete donor chimerism, platelet recovery remained incomplete, with counts gradually increasing only to approximately $30 \times 10^9/L$. The reported disappearance of the *THPO* variant from post-transplant blood sequencing merely reflects donor-derived hematopoiesis; the constitutional variant necessarily persists in non-hematopoietic tissues, including the recipient liver responsible for thrombopoietin production. Thus, this observation cannot be interpreted as molecular correction of the pathogenetic effects of the *THPO* deficiency. Of note, circulating thrombopoietin levels are not reported either before or after transplantation. Such measurements would have been particularly informative in this setting, as the p.R119C variant has previously been associated with inappropriately low circulating thrombopoietin levels,⁷ and complete donor hematopoietic chimerism is not expected to correct defective thrombopoietin production by recipient hepatocytes.

The subsequent response to avatrombopag is biologically compelling. Because MPL is intact in *THPO*-related CAMT, pharmacological MPL activation directly bypasses the deficient endogenous ligand, as previously reported with romiplostim.^{6,7} Avatrombopag may therefore represent an additional therapeutic option for these patients. Based on the reported clinical data, the specific contribution of avatrombopag, as compared with the other TPO-RAs administered, to the post-transplant hematological recovery remains difficult to ascertain. However, the sustained platelet counts above $100 \times 10^9/L$ during prolonged treatment strongly support further investigation of avatrombopag in *THPO* deficiency.

In conclusion, we would caution against the proposed model in which allo-HSCT and avatrombopag exert complementary therapeutic effects in *THPO*-mutated CAMT. The available biological and clinical evidence instead supports a genotype-directed distinction: allo-HSCT corrects the hematopoietic cell-intrinsic defect of *MPL*-related CAMT, whereas *THPO* deficiency is a hematopoietic cell-extrinsic disorder for which MPL agonists provide a rational targeted therapy.^{2,6,7} The present report provides interesting evidence supporting avatrombopag in this setting, but should not be interpreted as supporting allo-HSCT as part of the therapeutic strategy for *THPO*-related CAMT.

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