Cell Reports Medicine

CellPress
OPEN ACCESS

Spotlight

# Right in time: Mitapivat for the treatment of anemia in α- and β-thalassemia

Khaled M. Musallam,[1] Ali T. Taher,[2] and Maria Domenica Cappellini[3,*]
[1]Thalassemia Center, Burjeel Medical City, Abu Dhabi, United Arab Emirates
[2]Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon
[3]Department of Clinical Sciences and Community, University of Milan, Ca' Granda Foundation IRCCS Maggiore Policlinico Hospital, Milan, Italy
*Correspondence: maria.cappellini@unimi.it
https://doi.org/10.1016/j.xcrm.2022.100790

**Kuo and colleagues[1] evaluated the safety and efficacy of mitapivat, an oral pyruvate kinase activator, in adults with non-transfusion-dependent α-thalassemia or β-thalassemia. The high rate of hemoglobin response and good tolerability encourages further development in thalassemia.**

Kuo and colleagues[1] recently reported safety and efficacy data of mitapivat in adults with non-transfusion-dependent thalassemia (NTDT; α-thalassemia and β-thalassemia) from an open-label, multicenter, phase 2 study. The thalassemias are among the most common monogenetic diseases worldwide. They are recessively inherited disorders of hemoglobin production, classified into α- and β-thalassemia based on the affected globin gene. Most patients are found in the regional belt extending from the Mediterranean to South East Asia, although population migrations have introduced the disorder into large multiethnic cities in Northern Europe and the United States.[2] The hallmark of disease is ineffective erythropoiesis leading to a chronic hemolytic anemia, with a severity largely dependent on the type of inherited mutations and secondary molecular modifiers. The degree of anemia, among other factors, determines the need for transfusion therapy. Today, patients are recognized as having NTDT and transfusion-dependent thalassemia (TDT), as the transfusion requirement reflects the underlying pathophysiology and overall management needs.[2]

Patients with NTDT usually present later in childhood (compared to those with TDT, which are commonly diagnosed by the age of 2 years) with mild-to-moderate anemia. Accordingly, care providers have historically kept these patients transfusion independent except in specific clinical scenarios like infection, pregnancy, or surgery when occasional transfusions are administered or in cases requiring more frequent transfusions to manage specific morbidities.[3] This conservative approach to managing anemia in NTDT, however, is now being challenged with the expanding body of evidence linking low hemoglobin levels (<10 g/dL) to a high risk of serious morbidity and mortality in the long term, and the ability of increases by 1 g/dL to mitigate these risks.[4,5] Although transfusions remain an option, there is hesitancy to widely adopt such a strategy because of the associated clinical and economic burdens of regular transfusion requirements and secondary iron overload.[6,7] Thus, treating chronic anemia in individuals with NTDT remains a largely unmet medical need.

Mitapivat (AG-348) is a first-in-class oral, small-molecule, allosteric activator of the red blood cell (RBC)-specific form of pyruvate kinase (PK-R), which has shown efficacy and safety and has received US approval for the treatment of anemia in adults with PK deficiency.[8] In thalassemia mouse models, it reduced markers of ineffective erythropoiesis and improved anemia. In the featured phase 2 study,[1] 20 adults with NTDT (median age 44 years, 50% identifying as Asian; 15 with β-thalassemia and 5 with α-thalassemia) and a hemoglobin level ≤ 10 g/dL were enrolled to evaluate mitapivat's safety and efficacy in achieving a hemoglobin increase by ≥1.0 g/dL. Sixteen (80%) individuals had a response (5/5 in α-thalassemia and 11/15 in β-thalassemia). Favorable changes in markers of erythropoiesis and hemolysis were also noted. The most common treatment-emergent adverse events were initial insomnia (50%), dizziness (30%), and headache (25%).

These data are met with high enthusiasm considering the current absence of therapeutic options for the management of anemia in NTDT. The high hemoglobin response rate and favorable changes in markers of ineffective erythropoiesis are reflective of the drug's effect on the underlying pathophysiology. So, what is next for mitapivat? Two phase 3 double-blind, randomized, placebo-controlled, multicenter clinical trials are now underway in adults with NTDT (ENERGIZE, NCT04770753, n = 171) and TDT (ENERGIZE-T, NCT04770779, n = 240). The primary endpoint in ENERGIZE (NTDT) is hemoglobin response defined as a ≥1.0 g/dL increase in average hemoglobin concentration from week 12 through week 24 compared with baseline, while change in Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue Subscale will also be assessed. The latter is imperative considering the true benefits of anemia in reducing long-term morbidity and mortality in this patient population cannot be assessed in the context of clinical trials. Instead, the impact on short-term symptoms and patient-reported outcomes (PRO) can provide objective evidence of clinical benefit. Recently, the erythroid maturation agent luspatercept had its FDA application withdrawn in June 2022 for lack of agreement on benefit/risk.[9] In the BEYOND trial, luspatercept has shown a hemoglobin

response (≥1 g/dL increase) of 77% vs. 0% in placebo, but changes in a dedicated PRO tool for tiredness and weakness did not show statistical significance.[10] This may reflect the importance regulators are placing on showing a short-term PRO benefit, despite the proposed long-term benefits from treating anemia as a medical condition. Alternately, evidence of improvement in other markers of ineffective erythropoiesis or organ function could be considered. The extension of clinical development of mitapivat to patients with TDT is supported by its role in ameliorating ineffective erythropoiesis, the common underlying mechanisms in both NTDT and TDT patients. The primary endpoint in the ENERGIZE-T (TDT) study will be a transfusion reduction response defined as ≥50% reduction in transfused units with a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through week 48 compared with baseline.

Mitapivat comes in during an exciting and busy period of alternative therapeutics development for thalassemia; with several agents targeting various disease pathways. The aspect of mitapivat is that it is also being developed in patients with α-thalassemia, a truly orphan condition not only in therapeutic options but also in the evidence-base especially when compared to β-thalassemia. Irrespectively, as more agents become available to patients with thalassemia, it will be imperative to conduct head-to-head or combinatorial trials (between other agents or with conventional therapy) to inform the most appropriate treatment strategy for the individual patient profile. This would also need to be coupled with efforts to ensure access for all these advances in care in resource-limited geographies where the disease is highly prevalent.

## DECLARATION OF INTERESTS

K.M.M. reports consultancy fees from Novartis, Celgene Corp (Bristol Myers Squibb), Agios Pharmaceuticals, CRISPR Therapeutics, Vifor Pharma, and Pharmacosmos. M.D.C. reports consultancy fees from Novartis, Celgene Corp (Bristol Myers Squibb), Vifor Pharma, and Ionis Pharmaceuticals and research funding from Novartis, Celgene Corp (Bristol Myers Squibb), La Jolla Pharmaceutical Company, Roche, Protagonist Therapeutics, and CRISPR Therapeutics. A.T.T. reports consultancy fees from Novartis, Celgene Corp (Bristol Myers Squibb), Vifor Pharma, Silence Therapeutics, and Ionis Pharmaceuticals and research funding from Novartis, Celgene Corp (Bristol Myers Squibb), La Jolla Pharmaceutical Company, Roche, Protagonist Therapeutics, and Agios Pharmaceuticals.

## REFERENCES

1. Kuo, K.H.M., Layton, D.M., Lal, A., Al-Samkari, H., Bhatia, J., Kosinski, P.A., Tong, B., Lynch, M., Uhlig, K., and Vichinsky, E.P. (2022). Safety and efficacy of mitapivat, an oral pyruvate kinase activator, in adults with non-transfusion dependent alpha-thalassaemia or beta-thalassaemia: an open-label, multicentre, phase 2 study. Lancet *400*, 493–501. https://doi.org/10.1016/s0140-6736(22)01337-x.
2. Taher, A.T., Musallam, K.M., and Cappellini, M.D. (2021). β-Thalassemias. N. Engl. J. Med. *384*, 727–743. https://doi.org/10.1056/nejmra2021838.
3. Taher, A., Musallam, K., and Cappellini, M.D. (2017). Guidelines for the Management of Non Transfusion Dependent Thalassaemia (NTDT), 2nd ed. (Thalassaemia International Federation).
4. Musallam, K.M., Cappellini, M.D., Daar, S., and Taher, A.T. (2022). Morbidity-free survival and hemoglobin level in non-transfusion-dependent beta-thalassemia: A 10-year cohort study. Ann. Hematol. *101*, 203–204. https://doi.org/10.1007/s00277-020-04370-2.
5. Musallam, K.M., Vitrano, A., Meloni, A., Pollina, S.A., Karimi, M., El-Beshlawy, A., Hajipour, M., Di Marco, V., Ansari, S.H., Filosa, A., et al.; International Working Group on Thalassemia IWG-THAL (2022). Risk of mortality from anemia and iron overload in nontransfusion-dependent beta-thalassemia. Am. J. Hematol. *97*, E78–E80. https://doi.org/10.1002/ajh.26428.
6. Taher, A.T., Musallam, K.M., Karimi, M., El-Beshlawy, A., Belhoul, K., Daar, S., Saned, M.S., El-Chafic, A.H., Fasulo, M.R., and Cappellini, M.D. (2010). Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: The OPTIMAL CARE study. Blood *115*, 1886–1892. https://doi.org/10.1182/blood-2009-09-243154.
7. Musallam, K.M., Vitrano, A., Meloni, A., Pollina, W.A., Karimi, M., El-Beshlawy, A., Hajipour, M., Di Marco, V., Ansari, S.H., Filosa, A., et al. (2021). Survival and causes of death in 2, 033 patients with non-transfusion-dependent beta-thalassemia. Haematologica *106*, 2489–2492. https://doi.org/10.3324/haematol.2021.278684.
8. Grace, R.F., Rose, C., Layton, D.M., Galacteros, F., Barcellini, W., Morton, D.H., van Beers, E.J., Yaish, H., Ravindranath, Y., Kuo, K.H., et al. (2019). Safety and efficacy of mitapivat in pyruvate kinase deficiency. N. Engl. J. Med. *381*, 933–944. https://doi.org/10.1056/nejmoa1902678.
9. Bristol Myers Squibb (2022). Bristol Myers Squibb withdraws supplemental biologics license application (sBLA) for reblozyl (luspatercept-aamt) for non-transfusion dependent (NTD) beta thalassemia. https://investors.bms.com/iframes/press-releases/press-release-details/2022/Bristol-Myers-Squibb-Withdraws-Supplemental-Biologics-License-Application-sBLA-for-Reblozyl-luspatercept-aamt-for-Non-transfusion-Dependent-NTD-Beta-Thalassemia/default.aspx.
10. Taher, A.T., Cappellini, M.D., Kattamis, A., Voskaridou, E., Perrotta, S., Piga, A.G., Filosa, A., Porter, J.B., Coates, T.D., Forni, G.L., et al.; BEYOND Investigators (2022). Luspatercept for the treatment of anaemia in non-transfusion-dependent beta-thalassaemia (BEYOND): a phase 2, randomised, double-blind, multicentre, placebo-controlled trial. Lancet Haematol. https://doi.org/10.1016/S2352-3026(22)00208-3