[f] *Agios Pharmaceuticals, Inc., Cambridge, United States*
[g] *Department of Haematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark*
[h] *Haematology Unit, Department of Medicine, Hospital Pulau Pinang, Penang, Malaysia*
[i] *Thalassemia Unit, First Department of Pediatrics, National and Kapodistrian University of Athens, Athens, Greece*
[j] *São Paulo Blood Bank - GSH Group, São Paulo, Brazil*
[k] *Center for Research on Rare Blood Disorders (CR-RBD), Burjeel Medical City, Abu Dhabi, UAE*
[l] *Unità Operativa Semplice Dipartimentale Malattie Rare del Globulo Rosso, Azienda Ospedaliera di Rilievo, Nazionale, Cardarelli, Napoli, Italy*
[m] *Department of Haematology, Hospital Clínico Universitario Virgen de la Arrixaca-IMIB, Murcia, Spain*
[n] *Division of Hematology and Oncology, Department of Pediatrics, Weill Cornell Medicine, New York, United States*
[o] *Department of Pediatrics & Thalassemia Center, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[p] *Department of Clinical Sciences and Community, University of Milan, Ca'Granda Foundation IRCCS Maggiore Policlinico Hospital, Milan, Italy*
[q] *Division of Hematology, University of Toronto, Toronto, Canada*

Background: In thalassemia, ATP production in erythroid cells is too low to meet the demand of oxidative stress and ensuing cellular damage; this leads to ineffective erythropoiesis (IE) and chronic hemolytic anemia. Guidelines for non–transfusion-dependent thalassemia (NTDT) recommend raising hemoglobin (Hb) by ≥1 g/dL to reduce morbidities from IE and anemia. No oral disease-modifying therapies are approved for the treatment of β-thalassemia, and no agents are approved for α-thalassemia. Mitapivat is a first-in-class, oral, activator of pyruvate kinase that increases ATP production. Mitapivat may reduce metabolic stress, addressing the underlying pathophysiology across the full range of thalassemias, with the potential to reduce complications and improve health-related quality of life (HRQoL). **Aims:** To assess the efficacy and safety of mitapivat vs placebo (pbo) in adults with α- or β-NTDT in ENERGIZE (NCT04770753), a phase 3, double-blind, randomized, pbo-controlled, global trial. **Methods:** Adults (≥18 years) with α- or β-NTDT and baseline (BL) Hb ≤10 g/dL were randomized 2:1 to mitapivat 100 mg twice daily or pbo for 24 weeks (wks). NTDT was defined as ≤5 red blood cell (RBC) units transfused 24 wks before randomization and no RBC transfusions ≤8 wks before informed consent or during screening. The primary endpoint was Hb response: ≥1.0 g/dL increase in average Hb concentration over Wks 12–24 compared with BL. Key secondary endpoints were changes from BL in average Hb concentration and Functional Assessment of Chronic Illness Therapy–Fatigue Scale (FACIT-Fatigue) score over Wks 12–24. Safety and markers of hemolysis and erythropoiesis were among the secondary endpoints. **Results:** 194 patients (pts) were randomized (mitapivat n = 130; pbo n = 64); 94.8% completed the 24-wk trial. Mean age was 41.2 years, mean BL Hb was 8.3 g/dL, 86.6% received no transfusions in the 24 wks before randomization, and 32.0% had α-NTDT. BL characteristics were similar between treatment arms. Mitapivat demonstrated statistically significant improvements vs pbo for Hb response (42.3% vs 1.6%, respectively; 2-sided $p < 0.0001$), and for changes from BL in Wks 12–24 average Hb (least-squares mean [LSM] difference (95% CI): 0.96 g/dL (0.78, 1.15); 2-sided $p < 0.0001$) and Wks 12–24 average FACIT-Fatigue score (LSM difference (95% CI): 3.40 (1.21, 5.59); 2-sided $p < 0.0026$). Results favored mitapivat across all prespecified subgroups. Improvements in several markers of hemolysis and erythropoiesis were also observed, consistent with the proposed mechanism of mitapivat. The proportion of pts with treatment-emergent adverse events (TEAEs) of any grade was similar across treatment arms (mitapivat 82.9%; pbo 79.4%). The most common TEAEs (≥10% of pts) with mitapivat were headache, initial insomnia, nausea, and upper respiratory tract infection. Among mitapivat-treated pts, 6.2% had serious TEAEs (none considered treatment related) and 3.1% had TEAEs leading to treatment discontinuation; none occurred with pbo. **Summary/Conclusion:** Mitapivat significantly increased Hb and improved fatigue vs pbo; improvements were observed across all prespecified subgroups. Mitapivat was generally well tolerated with a low treatment discontinuation rate. These data are the first proof of efficacy of a disease-modifying therapy across the full range of NTDT (α- and β-thalassemia). Mitapivat may represent a new oral treatment option addressing both pathophysiology and HRQoL in thalassemia.

https://doi.org/10.1016/j.htct.2024.09.055

ANEMIA HEMOLÍTICA AUTOIMUNE EM PACIENTE DE 30 ANOS COM HEMOGLOBINA DE 1,9: RELATO DE CASO

RR Riboli, LZ Munhoz, AL Nunes, M Reinehr, J Fabião

Universidade Federal de Pelotas (UFPel), Pelotas, RS, Brasil

Introdução: Define-se anemia hemolítica autoimune pela presença de autoanticorpos que destroem eritrócitos ao ligarem-se em sua superfície. Classificada em primária ou secundária (a maioria dos casos) - associada a doenças linfoproliferativas, imunodeficiencias, neoplasias ou induzidas por medicações. Para realização do diagnóstico, deve-se considerar critérios laboratoriais: hemograma, reticulócitos, bilirrubinas, LDL, haptoglobina e o teste de Coombs direto. Espera-se nesses exames: anemia, reticulocitose, aumento do LDL, haptoglobina baixa e DAT +. A terapêutica se inicia com indicação de ácido fólico, glicocorticoides, pulsoterapia com imunoglobulina humana, rituximabe, ciclofosfamida, azatioprina, ciclosporina, micofelonato, danazol e esplenectomia. Nos casos secundários, realizar tratamento da causa base. **Objetivo:** Relatar quadro de anemia hemolítica autoimune que não

respondeu ao tratamento com corticoterapia e imunoglobulina humana, necessitando do uso de rituximabe e ciclofosfamida. **Relato de caso:** V.D.S.P, 30 anos, fisioterapeuta, tabagista. Conta que no dia 25/05 iniciou com astenia, esforço respiratório e taquicardia. Procurou assistência na UBS que orientou a realizar laboratoriais e US de abdome, evidenciando anemia (Hb 3,3) macrocítica e hipocrômica, e massa de origem abdominal a esclarecer. No momento da internação equipe clínica entrou em contato com hematologista do hospital que orientou prescrição de pulso com metilprednisolona 1 g/d por 5 dias e Imunoglobulina humana 500 mg/kg. No dia 31/05, paciente transferida para UTI em virtude de sintomas hipoxêmicos, hemoglobina de 1,9, reticulocitose 54% LDH 1118, TAD+, haptoglobina < 6 e icterícia às custas de BI. Assim, orientado Rituximabe 650 mg 1x/semana por 4 semanas. No dia 03/06, iniciada Ciclofosfamida 100 mg/d. Durante esse período observou-se melhora contínua dos índices hematimétricos e do estado geral da paciente. Realizou também reposição de vitamina B12 e ácido fólico. Submetida a biopsia percutânea de massa em retroperitônio cujo resultado evidenciou proliferação celular atípica. Solicitado exames laboratoriais que demonstraram: sorologias NR, toxoplasmose IgM NR, IgG reagente; herpes IgM NR, IgG reagente, anti-HTLV NR, parvovírus B19 NR; Fator reumatoide e FAN abaixo do valor de referência. Perfil de ferro e B12 dentro da normalidade. Exames de IGA, IGM e IGG dentro da normalidade. Em alta, paciente apresentava Hb de 9,1, reticulócitos de 6,3, LDH 248 - assintomática. Orientada seguir em uso de vitamina B12, ácido fólico e Ciclofosfamdia, com plano de redução via ambulatório. **Discussão:** Este relato de caso visa a discussão sobre definição clínica, critérios diagnósticos e tratamentos para paciente com anemia hemolítica autoimune. A literatura aponta que para definir como refratário ao manejo inicial do uso de corticotorepia, deve-se esperar o prazo de duas a três semanas. No entanto, considerando o grau de risco da doença, medidas conjuntas precisaram ser tomadas. O rápido diagnóstico e manejo dessa paciente foi essencial para que o desfecho fosse positivo. **Conclusão:** Este caso demonstra a importância de realizar o diagnóstico de anemia hemolítica autoimune, os passos clínicos e terapêuticos, visando a melhora do paciente e buscando o possível fator causal que desencadeou a hemólise, bem como o apoio fundamental do hematologista para resolução da clínica apresentada.

https://doi.org/10.1016/j.htct.2024.09.056

IMPROVEMENTS IN FATIGUE AND 6-MINUTE WALK TEST IN ADULTS WITH ALPHA- OR BETA-NON–TRANSFUSION-DEPENDENT THALASSEMIA: THE PHASE 3 ENERGIZE TRIAL OF MITAPIVAT

KH Kuo [a], H Al-Samkari [b], Y Aydinok [c], M Besser [d], S Gheuens [e], G Luna [f], A Glenthj [g], AS Goh [h], A Kattamis [i], SR Loggetto [j], KM Musallam [k], P Ricchi [l], E Salido-Fiérrez [m], S Sheth [n], V Viprakasit [o], MD Cappellini [p], AT Taher [q]

[a] *Division of Hematology, University of Toronto, Toronto, Canada*
[b] *Division of Hematology and Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, United States*
[c] *Department of Paediatric Haematology and Oncology, Ege University School of Medicine, Izmir, Turkey*
[d] *Department of Haematology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom*
[e] *Agios Pharmaceuticals, Inc., Cambridge, United States*
[f] *Centre de Référence Syndromes Drépanocytaires Majeurs, Thalassémies et Autres Pathologies Rares du Globule Rouge et de l'Érythropoïèse, Hôpital Henri Mondor APHP, Paris, France*
[g] *Department of Haematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark*
[h] *Haematology Unit, Department of Medicine, Hospital Pulau Pinang, Penang, Malaysia*
[i] *Thalassemia Unit, First Department of Pediatrics, National and Kapodistrian University of Athens, Athens, Greece*
[j] *São Paulo Blood Bank – GSH Group, São Paulo, Brazil*
[k] *Center for Research on Rare Blood Disorders (CRRBD), Burjeel Medical City, Abu Dhabi, UAE*
[l] *Unità Operativa Semplice Dipartimentale Malattie Rare del Globulo Rosso, Azienda Ospedaliera di Rilievo, Napoli, Italy*
[m] *Department of Haematology, Hospital Clínico Universitario Virgen de la Arrixaca-IMIB, Murcia, Spain*
[n] *Division of Hematology and Oncology, Department of Pediatrics, Weill Cornell Medicine, New York, United States*
[o] *Department of Pediatrics & Thalassemia Center, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[p] *Department of Clinical Sciences and Community, University of Milan, Ca'Granda Foundation IRCCS Maggiore Policlinico Hospital, Milan, Italy*
[q] *Division of Hematology and Oncology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon*

Background: Thalassemia, a group of inherited disorders characterized by ineffective erythropoiesis and chronic hemolytic anemia, is associated with wide-ranging impacts on health-related quality of life (HRQoL), such as impaired physical functioning and fatigue. Anemia has been associated with increased symptom burden and poor HRQoL in patients (pts) with non–transfusion-dependent thalassemia (NTDT). There are no available oral disease-modifying therapies that have been shown to improve HRQoL in β-thalassemia and no agents are approved for α-thalassemia. In a phase 2 study of pts with NTDT, improvements in hemoglobin were observed with mitapivat, a first-in-class, oral, allosteric activator of