RESULTS FROM A PHASE 2 STUDY OF MITAPIVAT IN ADULTS WITH NON –TRANSFUSION-DEPENDENT ALPHA- OR BETA-THALASSEMIA

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Objectives: Thalassemias are characterized by ineffective erythropoiesis and hemolysis due to imbalanced production and precipitation of globin chains. Adenosine triphosphate (ATP) levels are reduced in thalassemic red blood cells (RBCs), despite increased energy demands to maintain RBC cell integrity. Mitapivat (AG-348) is an oral activator of RBC pyruvate kinase (PKR), an enzyme regulating ATP production via glycolysis. In mice, mitapivat increased ATP synthesis and survival of thalassemic RBCs. Mitapivat has been shown to increase hemoglobin (Hb) in patients (pts) with PK deficiency and sickle cell disease. Results of the 24-week (wk) core period of a phase 2 open-label trial of mitapivat in adults with α- or β-non–transfusion-dependent thalassemia (NTDT; NCT03692052) are reported here. **Material and methods:** Key inclusion criteria: β-thalassemia $\pm\alpha$-globin gene mutations, Hb E β-thalassemia, or α-thalassemia (Hb H disease); Hb $\leq$10.0 g/dL; $\leq$5 RBC units transfused in prior 24 wks and none in prior 8 wks. Pts received mitapivat 50 mg orally twice daily (BID), then increased to 100 mg BID at Wk 6 visit, if tolerated. Primary endpoint was % pts who achieved a Hb response (increase $\geq$1.0 g/dL from baseline [BL] at any time between Wks 4–12, inclusive). Secondary endpoints included sustained Hb response ($\geq$2 Hb increases of $\geq$1.0 g/dL vs BL during Wks 12–24 after achieving a primary Hb response), time to first $\geq$1.0 g/dL Hb increase, markers of hemolysis and erythropoiesis, and safety. **Results:** Of 20 pts (15 female) who received mitapivat, the mean age (SD) was 45.3 (11.8) yrs (range 29–67); mean (SD) BL Hb was 7.9 (1.4) g/dL (range 5.1–9.8). At Wk 6, all pts were escalated to 100 mg BID. Nineteen pts (95.0%) completed the core period, one discontinued due to adverse event (AE);17 pts continued to the extension period. Sixteen pts (80.0%, 90% CI 59.9, 92.9; $p < 0.0001$) achieved a Hb response, including 5/5 pts with α-thalassemia and 11/15 pts with β-thalassemia. Mean (SD) time to first Hb increase >1.0 g/dL was 4.5 (3.2) wks, and mean Hb (SD) increase from BL during Wks 12–24 was 1.3 (0.6) g/dL. A sustained response was achieved in 65% of pts, including 5/5 pts with α-thalassemia and 8/15 pts with β-thalassemia. Hb increases occurred across the spectrum of BL levels. Directional improvements in markers of erythropoiesis and hemolysis were also observed. The safety profile was consistent with previously published mitapivat studies. There was one serious grade 3 unrelated AE of renal impairment, leading to treatment discontinuation. There were three non-serious grade 3 AEs leading to dose reduction: 1 resulted in a permanent dose reduction to 50 mg BID, and 2 were successfully rechallenged at 100 mg BID. The most common non-serious AEs occurring in $\geq$25% of pts were initial insomnia (10/20), dizziness (6/20), and headache (5/20). Dose escalation to 100 mg BID was well tolerated and not associated with any increase in AEs. Twelve pts had DXA scans at BL and 6 months; no notable changes in bone mineral density were observed. **Discussion:** These results demonstrate that PKR activation with mitapivat was well tolerated and improved anemia, hemolysis, and ineffective erythropoiesis, and may represent a novel therapeutic approach for pts with α- or β-thalassemia. **Conclusion:** The study met its primary endpoint with 80% of pts achieving a Hb response.

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SEQUESTRO HEPÁTICO SECUNDÁRIO A INFECÇÃO POR EPSTEIN-BARR EM CRIANÇA COM DOENÇA FALCIFORME

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Relato de caso: Paciente masculino, 4 anos e 10 meses, portador de Doença Falciforme (padrão SS), esplenectomizado devido a história prévia de sequestro esplênico, em uso regular de hidroxiureia e penicilina benzatina. Foi admitido com quadro de dor abdominal e crise álgica em ombro, sem outros sintomas associados, em bom estado geral, anictérico e corado, sem visceromegalias. Exames laboratoriais na admissão: Hb 10,3 g/dL, Ht 30,4%, leucócitos 32300/μL (segmentados 23% - 7429/μL, bastonetes 2% - 646/μL, linfócitos 66% - 21318/μL, linfócitos atípicos 5% - 1615/μL), plaquetas 332.000/μL, reticulócitos 7,1%, bilirrubina total (BT) 1,7 mg/dL, bilirrubina direta (BD) 0,2 mg/dL, bilirrubina indireta (BI) 1,5 mg/dL, desidrogenase lática (DHL) 972 U/L e proteína C reativa (PCR) 4,4. Optado por internação hospitalar para controle álgico e antibioticoterapia endovenosa (ceftriaxone). Após 72 horas, paciente evoluiu com febre, obstrução nasal, linfonodomegalia cervical, exsudato em orofaringe, palidez e icterícia progressivas, associado à colúria e a hepatomegalia palpável a 8 cm do rebordo costal direito (RCD). Solicitados novos exames laboratoriais: Hb 7,7 g/dL, Ht 22,3%, leucócitos 64590/μL (segmentados 13% - 8397/μL, linfócitos 40% - 25836/μL, linfócitos atípicos 44% - 28420/μL), plaquetas 169000/μL, reticulócitos 4%, BT 9,2 mg/dL, BD 7,7 mg/dL, BI 1,5 mg/dL, DHL 1770, PCR 6,5, fosfatase alcalina 514 U/L, gama-glutamil transferase (gama-GT) 327 U/L, proteínas totais 6,1, albumina 3,1, globulina 3, aspartato aminotransferase (AST) 467 U/L, alanina aminotransferase (ALT) 372 U/L. Aventadas hipóteses diagnósticas de sequestro hepático (queda de Hb e de plaquetas e aumento abrupto de fígado) e hepatite transinfecciosa (aumento de transaminases e BD, em vigência de quadro

infeccioso). Coletadas sorologias para hepatites virais, Epstein-barr (EBV) e citomegalovírus e modificado antibioticoterapia para metronidazol e cefotaxima. Realizada transfusão de concentrado de hemácias (10 mL/kg), com Hb de 9,9 g/dL e redução de hepatimetria para 4 cm do RCD após, evoluindo também com melhora progressiva do estado geral, da icterícia e da colúria. Resultado de sorologia IgM positivo para EBV, confirmando o diagnóstico infecção por Epstein-barr como gatilho para o sequestro hepático. Recebe então alta hospitalar após 13 dias de internação, com melhora dos exames laboratoriais para seguimento ambulatorial com especialidades. **Discussão:** As hepatopatias agudas, apesar de pouco frequentes, podem ocorrer como complicações relacionadas a doença falciforme. Dentre essas manifestações está o sequestro hepático, definido como queda de Hb >2 g/dL, dor abdominal e aumento abrupto do fígado. Infecções pelo EBV são reconhecidas como fatores desencadeante de quadros hepáticos agudos, principalmente hepatites, porém existem poucos relatos na literatura de associação com sequestro hepático. Desta forma, o caso apresentado deixa claro que diante de alterações hepáticas agudas em pacientes com Doença Falciforme e sinais de infecções virais como EBV deve-se atentar para o risco e diagnóstico de sequestro hepático associados; realizando prontamente a transfusão como suporte de tratamento e reduzindo morbimortalidade nessa população.

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SICKLE CELL DISEASE MORTALITY IN BRAZIL: A SINGLE-CENTER EXPERIENCE

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Introduction: Sickle cell disease (SCD) is one of the most frequent genetic disorders in the world, making it a public health problem in several countries. Nevertheless, there are still few data regarding mortality of this population in Brazil. **Methodology:** This is a retrospective, epidemiological and descriptive study of mortality from sickle cell disease at the regional level. The sample consisted of living and deceased patients followed at the hemoglobinopathies outpatient clinic at the Reginal Blood Center of Ribeirão Preto between the years 2005 and 2020. The data were obtained from physical or electronic medical records linked to the Medical School of Ribeirão Preto Clinical Hospital. **Results:** 54 deaths occurred among 641 patients (37 in SS, 6 in SB0, 10 in SC and 1 in SD). The overall death rate was 8.4% and the annual general death rate was 0.56%. Surprisingly, the mortality rate among children below 5 years old was zero, and 1.8% in children below 18 years old. Patients with HbSS/SB had a higher death rate (9.4%, 0.62%/year) compared to SC patients (5.7%, 0.38%/year, $p = 0.005$). The mean age at death was 38.6/36.6 years for the SS/SB group and 44 years for the SC group. Prior to death, patients had a mean of 2.4 complications, 3.5 in the SS/SB group and 1.7 in the HbSC group. The most common cause of death was acute chest syndrome (50%), followed by pulmonary thromboembolism and sepsis (9.20% each). **Discussion:** Despite advances in the understanding of pathophysiology, causes of death and treatment, morbidity and mortality in SCD still remain a clinical challenge, especially in middle-income countries such as Brazil. Nevertheless, our results are more similar to high-income countries than published data from other regions in Brazil. Neonatal screening, antibiotic prophylaxis, close follow up since diagnosis and early treatment may have contributed to the reduction of mortality in our sickle cell population. **Conclusions:** In our centre, young patients with SCD have a low mortality rate, comparable to what is observed in high-income countries. SS/SB patients, as expected, present a higher mortality rate than SC patients. Herein, we believe to have shown that in Brazil it is possible to improve survival rates in patients with SCD.

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SÍNDROME CORONARIANA AGUDA E ANEMIA HEMOLÍTICA AUTOIMUNE EM PACIENTE COM MACROGLOBULINEMIA DE WALDENSTRÖM: RELATO DE CASO

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Introdução: A macroglobulinemia de Waldenström (MW) é um linfoma indolente, resultante do acúmulo, predominantemente na medula óssea, de linfócitos plasmocitoides monoclonais malignos que secretam imunoglobulina M (IgM) monoclonal. **Relato do caso:** M.A.C.L., 73 anos, masculino, médico, natural e procedente de João Pessoa – PB. Paciente chega ao serviço de urgência em 07/08/2019, queixando-se de dor retroesternal, associada a náusea e dispneia aos esforços habituais, que alivia com repouso. Apresenta história pessoal de diabetes mellitus, hipertensão arterial e doença arterial coronariana há 20 anos. Foi solicitado ECG de repouso, compatível com Síndrome Coronariana Aguda (SCA) Sem Supradesnivelamento do Segmento ST. Iniciou-se protocolo para SCA. Paciente foi admitido na Unidade de Terapia Intensiva e foram solicitados hemograma, TAP e TTPA (Hb 5,2 VCM 132 L 24200 N 12584 Plaquetas 242 mil TAP 42% TTPA 48), quando foi constatada dificuldade de analisar os hemogramas