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Abstract Book for the 17th Annual Sickle Cell and Thalassaemia Conference

ORAL PRESENTATIONS

001 Basic and Translational Abstracts

5595849 THE GUT MICROBIOME AND HYDROXYUREA EFFECT ON SICKLE CELL DISEASE CHILDREN FROM ANGOLA

Brito, M.; Delgadinho, M.; Ginete, C.; Santos, B.; Vasconcelos, J.

Background: Sickle cell disease (SCD) is an inherited hematological disorder and a serious global health problem, affecting between 20 and 25 million people worldwide [1]. In the Sub-Saharan Africa, where it is more prevalent, it contributes up to 90% of under-5 mortality [2]. Although hydroxyurea (HU) is the leading treatment for these patients, its effects on the gut microbiome have not yet been explored. Some studies reported that gastroenteritis events were less frequent in SCA children taking HU and it also significantly improved the survival from pneumococcal infections [3,4]. HU may have a protective effect, not only by improving several hematological parameters but also by lowering the risk of some bacterial infections.
Aims: In this context, the aim of this study was to investigate this association by characterizing the gut microbiome of an Angolan SCA pediatric population before and after 6 months of HU treatment and comparing with a control group of healthy siblings.
Results: A total of 113 fecal samples were obtained and sequenced by NGS for the 16S rRNA gene (V3-V4 regions), which corresponded to 40 children in the control and before HU groups and 33 after HU, aged between 4-12 years old. Our findings revealed that these three groups exhibit some notable differences, especially within *Lachnospiraceae* and *Ruminococcaceae* family. After HU treatment there was an increase of several beneficial bacteria, such as: *Blautia coccoides* (p=0.009), *Blautia luti* (p<0.001), *Blautia faecis* (p=0.008), *Bifidobacterium longum* (p=0.011), *Dorea formicigenerans* (p<0.001), *Dorea massiliensis* (p=0.003), *Eubacterium halii* (p=0.004), *Elusimicrobium spp* (p=0.032), *Ruminococcus callidus* (p=0.037), *Ruminococcus faecis* (p=0.012), *Roseburia spp* (p=0.050) *and Subdoligranulum variabile* (p=0.009). Most of those OTUs are SCFAs producing species, having butyrate or propionate as end-products of bacterial metabolism, both exhibiting anti-inflammatory properties. Moreover, children before HU had higher abundance of bacteria considered pathogenic, like *E. coli* (p=0.001), *Clostridiun_g24* (p=0.039) *and H. influenzae* (p=0.050).
Conclusion: Overall, this study provides the first evidence of the HU effect on the gut microbiome and provides a rationale for further research for developing treatments to reduce gut microbiota-driven inflammation, which may attenuate the dysbiosis and chronic symptoms experienced by these patients. This work was supported by FCT/Aga Khan (project n°330842553) and FCT/MCTES (UIDB/05608/2020 and UIDP/05608/2020) –H&TRC.

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002 Novel Therapies, Gene Therapies and Bone Marrow Transplant and Emerging Diagnostics Abstracts

5589320 FOLLOW-UP RESULTS OF A PHASE 2 STUDY ASSESSING THE SAFETY AND EFFICACY OF MITAPIVAT TREATMENT, AN ORAL PYRUVATE KINASE ACTIVATOR, FOR UP TO 60 WEEKS IN SUBJECTS WITH SICKLE CELL DISEASE

van Dijk, M.J.; Rab, M.A.E.; van Oirschot, B.A.; Bos, J.F.; Derichs, C.; Rijneveld, A.W.; Cnossen, M.H.; Nur, E.; Biemond, B.J.; Bartels, M.; Jans, J.J.M.; van Solinge, W.W.; Schutgens, R.E.G.; van Wijk, R.; van Beers, E.J.

Background: Sickle cell disease (SCD) is a devastating red blood cell (RBC) disorder. The root cause of SCD is polymerization of sickle hemoglobin (HbS) upon deoxygenation, resulting in poorly deformable sickled RBCs with shortened lifespan. 2,3-diphosphyglycerate (2,3-DPG), a glycolytic intermediate in RBCs, promotes deoxygenation by lowering hemoglobin (Hb)-oxygen affinity. Mitapivat (AG-348) is an oral allosteric activator of pyruvate kinase (PK), a key enzyme in RBC glycolysis generating adenosine triphosphate (ATP) and reducing 2,3-DPG levels.
Aims: To report follow-up data of the safety and efficacy of mitapivat treatment in subjects with SCD (ESTIMATE study; www.trialregister.nl NL8517; EudraCT 2019-003438-18).
Methods: The ESTIMATE study is a phase 2, investigator initiated, open-label study. Subjects ≥16 years with SCD (HbSS, HbS/β^0 or HbS/β^+), 1-10 vaso-occlusive crises (VOCs) in the prior year and/or prior SCD-related complications, a Hb level >6.1 g/dL and ≤11.1 g/dL, and no chronic transfusions are eligible and treated with mitapivat after obtaining informed content. In the 8-week dose finding period, initial dosing is 20 mg twice daily, escalated to max. 100 mg twice daily, and followed by an up to 52-week fixed dose extension period (FDEP). Primary endpoints are safety, based on adverse events (AEs), and efficacy of mitapivat treatment on RBC sickling (Point of Sickling (PoS), oxygen gradient ektacytometry). Key secondary endpoints are changes in Hb level, markers of hemolysis, ATP/2,3-DPG levels, and Hb-oxygen affinity (p50, Hemox Analyzer).
Results: Until Jan. 2022, 9 subjects were treated with mitapivat. Baseline characteristics were: median age 22 years (range 16-59 years), 6/9 (67%) female, and 6/9 (67%) used hydroxyurea. 7/9 (78%) had HbSS, 1/9 (11%) had HbS/β^0, and 1/9 (11%) had HbS/β^+. One subject with a non-treatment related serious AE (SAE) of a urinary tract infection (grade 4), was lost to follow-up shortly after first dosing. No other SAEs or treatment-emergent AEs (TEAEs) grade ≥3 occurred. The remaining 8 subjects had a median treatment duration of 38 weeks (range 11-60 weeks). 6/8 (75%) took 100 mg mitapivat twice daily in the FDEP, and 2/8 (25%) took 50 mg mitapivat twice daily after a single dose reduction because of progressive transaminase increase. The most common TEAEs were (n>2 subjects): ALT or AST increase (both 5/9, 56%; all grade 1), and headache (4/9, 44%; grade 1-2). Three VOCs occurred: one related to excessive alcohol consumption with no need for hospitalization, and two in subjects with documented noncompliance the week before hospitalization. Mean annual VOC rate and SCD-related hospital admission days were, respectively, 1.5±1.3 and 5.9±7.1 days at baseline, and reduced to 0.5±0.7 and 1.6±3.1 days when weighting