HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

P1483 EPELEUTON, A NOVEL SYNTHETIC SECOND GENERATION W-3 FATTY ACID, PROTECTS HUMANIZED SICKLE CELL MICE AGAINST HYPOXIA/REOXYGENATION ORGAN DAMAGE

Topic: 26. Sickle cell disease

Enrica Federti[1], Alessandro Matte'[1], Moayed Hamza[2], Adam Lafferty[2], David Coughlan[2], Markus Weissbach[2], Deepak L. Bhatt[3], Veronica Riccardi[1], Rachele Perissinotto[1], Angela Siciliano[1], John Climax[2], Carlo Brugnara[4], Lucia De Franceschi[1]

[1] Dept of Medicine, University of Verona, Verona, Italy;[2] Afimmune Ltd, Dublin, Ireland;[3] Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, United States;[4] Dept of Laboratory Medicine, Harvard Medical School, Boston, United States

Background: Sickle cell disease (SCD) is a hereditary red cell disorder with high mortality and morbidity. Although crizanlizumab, a P-selectin inhibitor, and voxelotor, an oral anti-sickling agent, have been recently approved for clinical management of SCD, therapeutic options to limit acute events and to reduce disease progression are still required. An attempt to target inflammatory vasculopathy and to modulate inflammatory response has been made based on evidence in other diseases such as in cardiovascular disease looking to administration of ω-3 fatty acids. In humanized SCD mice, we previously showed that polyunsaturated fatty acid supplementation protects against acute sickle cell-related lung and liver damages during hypoxia/reoxygenation (H/R) induced vaso-occlusive crisis (VOCs) (Kalish B et al. Haematologica 2016). This agrees with the observation that the resolution process actively controlled by specialized pro-resolving lipid mediators is defective in SCD (Matte A et al, Blood 2019).

Epeleuton (15-HEPE, 15 hydroxy eicosapentaenoic acid) is a novel synthetic second generation w-3 fatty acid which (i) has a favorable clinical safety profile, (ii) modulates systemic inflammation and triglyceride synthesis in patients with cardiometabolic disease (Climax J et al J Am Heart As 2020) and (ii) beneficially affects red cell indices in long-term studies in rats.

Aims: To evaluate the impact of epeleuton on acute organ damage in a humanized mouse model of SCD.

Methods: 3-4 month old male and female mice healthy control (Hbatm1(HBA)Tow Hbbtm3(HBG1,HBB)Tow) and Tim Townes sickle mice (SCD, Hba $^{tm1(HBA)Tow}$ Hbb $^{tm2(HBG1,HBB*)Tow}$) were used. Animals were treated for 6 weeks with epeleuton 1,000 mg/kg once daily or vehicle by gavage. Mice underwent 10 hours of hypoxia (8% oxygen), followed by 3 hours of reoxygenation (21% oxygen) to mimic acute VOCs (Matte A et al, Blood 2019). Hematologic parameters and molecular analysis of target organs for SCD such as lung were carried out.

Results: In SCD mice exposed to H/R stress, we found that epeleuton (i) reduces H/R induced hemolysis; (ii) normalizes tyrosine-phosphorylation profile of red cell membrane proteins; and (iii) decreases neutrophil count. In lungs of SCD mice exposed to H/R stress, we observed that epeleuton prevents the H/R induced activation of inflammatory and redox related transcription factors NF-kB, p65 and Nrf2 local inflammatory response compared with vehicle-treated animals. Epeleuton treated SCD mice exposed to H/R stress showed down-regulation of VCAM-1 and E-selectin, markers of inflammatory vasculopathy as well as reduction of lung protein oxidation and expression of anti-oxidant systems such as heme-oxygenase-1 (HO-1) or peroxiredoxin-2. Similar changes were also observed in livers of epeleuton-treated SCD mice exposed to H/R stress compared with vehicle-treated SCD animals. Of note, epeleuton prevented the H/R induced up-regulation of both VCAM-1 and ICAM-1, suggesting a direct impact of treatment on vascular activation and inflammation.

Summary/Conclusion: In humanized SCD mice exposed to H/R stress to mimic acute VOCs, epeleuton acts as a multimodal agent targeting red cells, hemolysis, inflammatory response, and vascular dysfunction. Our data provide the rationale for epeleuton as a potential novel therapeutic option for clinical management of patients with SCD.