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POSTER ABSTRACTS

114.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Effects of L-Glutamine on Biomarkers of Response in Sickle Cell Disease: A Pharmacokinetics-Pharmacodynamics Analysis

Alina Sadaf, MBBS[1], *Min Dong, PhD*[2], *Jennifer Korpik*[1], *Amanda Pfeiffer*[1], *Theodosia A. Kalfa, MDPhD*[3], *Teresa S. Latham, MA*[1], *Alexander A. Vinks, PharmD, PhD FCP*[4], *Russell E. Ware, MD PhD*[1], *Charles T. Quinn, MD*[5]

[1] Division of Hematology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
[2] Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
[3] Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
[4] Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH
[5] Division of Hematology, Cincinnati Children's Hospital Med. Ctr., Cincinnati, OH

OralL-glutamine (Endari®) has been approved by the US-FDA to reduce the acute complications of sickle cell disease (SCD) in patients at least 5 years of age. L-glutamine has several roles in the body including *de novo* synthesis of intracellular glutathione which acts as an antioxidant. However, the mechanisms of action by which L-glutamine could reduce complications in SCD require further investigation. Additionally, there are no known biomarkers to assess response to L-glutamine therapy. We conducted an open-label, dose-ascending trial (NCT04684381) of L-glutamine in pediatric (n=4) and adult (n=4) participants with SCD as well as in adult healthy volunteers (n=4) (Table 1). Over a three-week trial period with 4 study visits, serial blood samples were collected to define the pharmacokinetics (PK), pharmacodynamics (PD), and PK-PD interactions of L-glutamine using a broad panel of laboratory investigations including amino acid concentrations, blood counts, percentage of dense red blood cells (%DRBC), whole blood viscosity, osmotic and oxygen gradient ektacytometry, and reactive oxygen species (ROS) of reticulocytes (ROS_{retic}) and mature red blood cells (ROS_{RBC}).

In PK-PD analysis of amino acids, we focused analysis on arginine (Arg), citrulline (Cit), and ornithine (Orn) based on the hypothesis that L-glutamine improves endothelial function by increasing arginine bioavailability and augmenting nitric oxide (NO) production. Peak arginine concentration was directly correlated with both the maximum L-glutamine concentration (C_{max} p=0.001) and area-under-the curve (AUC) (p=0.047) indicating improvement in arginine bioavailability, but there was no significant linear correlation with either the Arg:Orn or Arg:(Orn+Cit) ratios.

In PK-PD analysis of osmotic gradient ektacytometry, L-glutamine C_{max} was directly correlated with the elongation maximum (EI_{max}), noted in all participants at visit 4 (p=0.033). In SCD participants, L-glutamine C_{max} was inversely correlated with O_{hyper} (osmolality at $EI_{max}/2$) at visits 3 (p=0.044) and 4 (p=0.004). In PK-PD analysis of oxygen gradient ektacytometry in SCD participants, L-glutamine C_{max} was inversely correlated with the point of sickling (POS) at visit 3 (p=0.005) but not at visit 4 (p=0.054). Together, these findings suggest that although L-glutamine may decrease cellular hydration (decreased O_{hyper}) it may increase RBC deformability (increased EI_{max}) and delay the onset of sickling after hypoxia (decreased POS).

In PK-PD analysis of viscometry, higher L-glutamine C_{max} was associated with higher whole blood viscosity measurements at all shear rates ($p<0.05$). However, L-glutamine C_{max} was also directly correlated with hematocrit-to-viscosity ratio (HVR) at the highest shear rates in the overall population at visit 4 ($p<0.05$). In addition, L-glutamine C_{max} for SCD participants was associated with increased hemoglobin concentration, an effect that was observed at visit 4 (p=0.025), and increased %DRBC, an effect detected at visits 3 (p=0.008) and 4 (p=0.007).

In PK-PD analysis of ROS, L-glutamine AUC was inversely correlated with ROS_{Retic} (p=0.024), but not ROS_{RBC}, in all participants at visit 3. When considered as total ROS_{Retic} (calculated as ROS_{retic} × absolute reticulocyte count), there was a similar inverse correlation with glutamine AUC in SCD participants, although not statistically significant. In contrast to all other biomarkers, L-glutamine C_{max} was not correlated with any ROS measurement.

This PK-PD analysis of L-glutamine reveals biological effects that alter RBC characteristics and could modify SCD-related complications, with a complex interplay summarized in Figure 1. Prospective studies can validate these biomarkers and be used to monitor the effects of L-glutamine therapy in SCD patients.

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Table 1. Characteristics of Participants.

	Pediatric SCD	Adult SCD	Healthy Volunteers
Number	4	4	4
Age *mean (min-max)*	12.0 (6.8 - 15.1)	23.5 (20.4 - 29.3)	37.3 (29.6 - 43.8)
Sex (N)	Female (2) Male (2)	Female (3) Male (1)	Female (3) Male (1)
Weight (kg) *mean (min-max)*	64.3 (30.3 - 101.5)	63.45 (49.3 - 72.8)	105.1 (67.5 - 119.1)
Hb phenotype (N)	SS (2) SC (2)	SS (2) SC (2)	AA (4)
Hydroxyurea use (N)	Yes (2) No (2)	Yes (2) No (2)	N/A
Hb (g/dL) *mean (min-max)*	9.4 (7.8 - 11.2)	9.9 (8 - 13.1)	14.0 (13.1 - 15.8)
ARC ($x10^3$/mL) *mean (min-max)*	314 (122 - 506)	184 (28 - 374)	61 (41-81)
Hb F (%) *mean (min-max)*	8.8 (2.5 - 15.3)	14.7 (0 - 35.3)	N/A
F-cells (%) *mean (min-max)*	35.5 (11.3 - 59.3)	42.3 (1.5 - 92.1)	N/A
Alpha-globin genotype	αα/αα (N=3) αα/–α (N=1)	αα/αα (N=3) –α/–α (N=1)	N/A

Abbreviations: ARC, absolute reticulocyte count; Hb, hemoglobin; Hb F, fetal hemoglobin; F-cells, Hb F containing red blood cells; N/A, not applicable.

Figure 1. Therapeutic balance of glutamine in SCD. Pharmacokinetics-pharmacodynamics (PK-PD) analysis revealed several biological effects associated with glutamine C_{max} or AUC. As shown, some effects of higher glutamine exposure could theoretically exacerbate or ameliorate the disease, while some could have uncertain net effect. Increased Hb and Hct could increase oxygen carrying capacity but increase viscosity, and increased dense red blood cells (DRBC) could reflect increased generation or increased lifespan of DRBCs. Effects seen only in the overall population are shown in gray. The balance of these biological effects in each patient likely determines the therapeutic response and its degree to glutamine. Abbreviations: Arg:Orn, arginine:ornithine ratio; AUC, area under the curve; C_{max}, maximum glutamine concentration; DRBC%, percent DRBC; EI_{max}, maximum elongation index; Hb, hemoglobin; Hct, hematocrit; HVR, hematocrit:viscosity ratio; O_{hyper}, osmolality at $EI_{max}/2$; POS, point of sickling; ROS_{Retic}, reticulocyte reactive oxygen species.

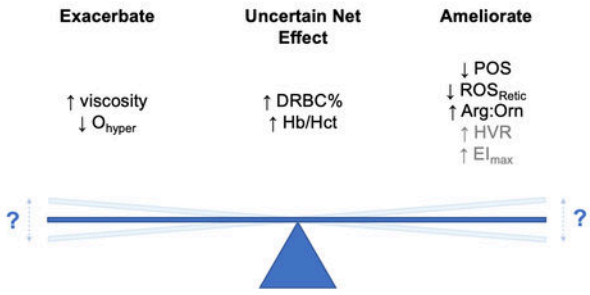

Figure 1

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