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A phase-3 study of L-glutamine therapy for sickle cell anemia and sickle ß^0-thalassemia

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Abstract

Background: New treatments for patients with sickle cell disease (SCD) are needed. Oxidative stress may lead to disturbance of cell membranes, exposure of adhesion molecules and damage to the contents of the sickle red blood cells (s-RBC). Nicotinamide adenine dinucleotide (NAD) molecules modulate oxidation-reduction in s-RBCs. Our previous laboratory work demonstrated enhancement of NAD in s-RBC by supplementing a precursor of NAD, L-glutamine. In our Phase-2 clinical study in SCD, oral prescription grade L-glutamine (PGLG) signaled a decreasing trend for painful crises at 24 weeks and a significant decrease in hospitalization at 24 weeks.

Methods: A randomized (2:1) Phase 3 placebo-controlled trial was conducted across the United States. Subjects were stratified by hydroxyurea usage. Eligibility criteria included patients ≥5 years of age with diagnoses of HbSS or HbS/β^0-thalassemia with at least two episodes of sickle cell crises (SCC) during the 12 months prior to screening. PGLG at 0.6 g/kg/day (max 30 g), or placebo, was self-administered in two divided doses orally. The primary endpoint was number of SCC; secondary endpoints included rates of hospitalization and adverse events; additional analyses included cumulative hospital days, incidence of acute chest syndrome (ACS) and time to first crises.

Results: A total of 230 patients were enrolled at 31 sites. Groups were well balanced for clinical characteristics. The median incidence of SCC (3 vs. 4 events; p=0.008) as well as hospitalizations (2 events vs. 3; p=0.005) was significantly lower in the treatment group compared to the placebo group. Median cumulative hospital days were lower by 41% in the treatment group (6.5 days) vs. the placebo group (11 days) (p=0.022); ACS was 11.9% in the treatment group and 26.9% in the placebo group (p=0.006). The median time to first crisis was 87 days in the treatment group vs. 54 days in placebo group (p=0.010). Analysis by hydroxurea use, age, and gender yielded consistent findings. Adverse events in the treatment arms were similar between groups.

Conclusion: This Phase-3 study in SCD demonstrated that treatment with PGLG provided clinical benefit over placebo by reducing the frequency of painful crises and hospitalization. Additional benefit was observed when evaluating ACS, time to first crises and duration of hospital stay. PGLG was relatively easy to administer and did not require special monitoring.

Biography

Yutaka Niihara has been involved in patient care and research for sickle cell disease for most of his career, and is the Principal Inventor of the patented L-glutamine therapy for treatment of sickle cell disease. He is a Co-founder of Emmaus, Principal Investigator for LABioMed at Harbor-UCLA Medical Center and Professor of Medicine at the David Geffen School of Medicine at UCLA. His experience includes serving as President, Chief Executive Officer and Medical Director of Hope International Hospice. A board-certified by the American Board of Internal Medicine and the American Board of Internal Medicine/Hematology, he is licensed to practice medicine in both the U.S. and Japan. His honors include the Life Time Achievement Award, from the Sickle Cell Disease Foundation of California and the Abigail Kawananako Award. He received his BA in Religion from Loma Linda University and obtained his MD degree from the Loma Linda University School of Medicine.