

Safety Trial of a Secretory Phospholipase A2 Inhibitor in Sickle Cell Disease

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A. Specific Aims

As originally submitted, our grant outlined a study to assess the safety of a phospholipase (sPLA2) inhibitor in sickle cell patients at risk for acute chest syndrome and entailed the use of a specific inhibitor of sPLA2, LY315920, then produced by Eli Lilly. Since submission and funding of the grant, Lilly halted production of the drug because it failed to show efficacy in a large sepsis trial. The drug then became unavailable to us for use in our original study. At that time there was no other specific inhibitor to sPLA2 type IIa available for human trials. The only drug that had been shown to inhibit sPLA2 in humans was Remicade (infliximab) which is an anti-TNF chimeric antibody. In a small study, patients with Crohn's disease were given a single dose of Remicade and sPLA2 production was completely inhibited within 24 hours. Remicade was already approved for use in patients with rheumatoid arthritis and Crohn's disease. Given the lack of the specific inhibitor to sPLA2, we designed a new study using infliximab to determine if infliximab can inhibit the production of sPLA2. This new study was a pilot, dose-escalating study of infliximab in sickle cell patients who are admitted with vaso-occlusive crisis and who have a sPLA2 level greater than 100ng/ml. Patients were to receive one of four doses of infliximab to determine if a single dose of infliximab will inhibit the production of sPLA2. Patients began with a dose of 2 mg/kg/dose and this dose is not effective then the next group of patients will escalate to 5mg/kg/dose. Similarly if this dose was not effective then patients would increase to 8mg/kg/dose and then 10mg/kg/dose. Infliximab was said to be effective if there is a 50% reduction in sPLA2 levels by Hour 48 and if the level remained less than 50% at Day 5.

This new study design was reviewed by the Steering Committee, Protocol Review Committee and the Data Safety and Monitoring Board of the NHLBI. In February of 2005, the DSMB gave final approval pending FDA concurrence on an Investigational New Drug Waiver. An FDA application was submitted and by June of 2005 they had issued a letter of concurrence that this study was exempt from IND regulations. Local Investigational Board approval was obtained in April of 2005. As of June 2005 the study was clear to enroll patients. The assay for sPLA2 was re-initiated and local medical personnel informed of the availability of the assay in early Summer of 2005. Screening began in August 2005.

B. Studies and Results

In August 2005, routine screening with the sPLA2 assay was begun. Two patients were enrolled in the study and were treated with the lowest dose of infliximab. Final data is pending on the most recent patient enrolled in the study. In order to improve the efficiency of the assay and extend screening to weekends, we recently developed a sPLA2 assay for the chemical analyzer.

This novel sPLA2 activity assay was developed for the use in the clinical laboratory on the Chem Analyzer. Dr. Kuypers is currently developing an ELISA based assay for the clinical laboratory. Together both the activity assay as well as the protein level assay (ELIOSA) can be used to screen patients at risk for the development of ACS, and can be used if chosen so for multi center studies, with the ultimate goal to provide the clinical labs in hospitals serving the sickle cell patient community with a powerful tool to predict and prevent the major cause of mortality in these patients.

The infliximab study has been permanently halted at CHRCO and we plan to pursue our original research plan in the context of the new Anthera clinical trial with the specific sPLA2 inhibitor. The Anthera trial was submitted and has received full IRB approval at our site. Screening with an Anthera-developed sPLA2 ELISA is now underway and we recently enrolled our first subject. We will proceed with the laboratory research component of original study after approval from NHLBI staff. Budget changes will be made as the patient care costs originally allotted in the grant will now be covered by Anthera..