Vitamin E for NASH Treatment in HIV Infected Individuals

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Statistical Plan

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Statistical Considerations

Because host genetic factors contribute to the response to therapy, pre-therapy baseline liver expression profiles will be studied to identify expression signature that predict response to vitamin E therapy. This approach has been used in other liver disease such as hepatitis C. For example, in one study, pre-treatment peripheral blood monocytes gene expression signature predicted response to hepatitis C therapy with 94% accuracy (143).

Quantitative global gene expression analysis on fresh frozen liver tissue from subjects participating in the clinical trial will be performed. Based on prior experience, it is expected to have a portion of the liver biopsy snap frozen and available for expression analysis on a sizable proportion of the subjects (>50%) undergoing liver biopsies as part of Specific Aim 2 who are the primary source for the proposed clinical trial. As such, HumanHT-12 v4 Expression BeadChip will be used for this aim. This chip provides genome-wide transcriptional coverage of well-characterized genes and their splice variants, and targets more than 47,000 probes derived from the NCBI RefSeq Release 38 (November 7, 2009) and other sources.

After detectable transcripts are identified, expression data will be standardized. The t- test statistic will be utilized to measure the expression difference between the sample means (responders vs. non-responders) in units of the standard deviation for which the difference can be tested using certain p value. For this, a significance cut-point of $p<0.001$ will be used. Then hierarchical clustering and gene network and pathway analysis will be performed to identify those predicting response to vitamin E therapy. A logistic multivariate-based analysis will be used to build up a receiver operating characteristic (ROC) curve, and the area under the ROC curve (AUC) will be calculated to assess the average sensitivity of the biomarker in discriminating the responders and non-responders.

All endpoints are measured as the change from baseline to 24 weeks. The primary outcome measure is the change in hepatic fat content as measured by central reading of MR-PDFF performed at baseline and end of study. Secondary endpoints will be changes in inflammatory markers (liver enzymes, TNF-alpha, IL-10 levels), serum K-18, Liver stiffness and CAP measurement by TE, and MDA level as a marker of oxidative stress.

The primary outcome is the improvement in liver fat as assessed by MR-PDFF at end of treatment compared to baseline. To our knowledge, there are no data on studying the effect of vitamin E on MR-PDFF in NASH patients with HIV. Using an alpha of 5% and a two-sample independent t-test and equal variance assumption, a sample size of 25 per group will have 91% power to detect an effect size of 0.97 and will have 80% power to detect an effect size as small as 0.81. To ensure this number is achieved, 28 subjects per group will be recruited, allowing for 10% drop-out during the trial. The primary purpose of this pilot study is to generate preliminary data to estimate the mean and variability of improvement in liver fat with vitamin E in HIV infected patients with NASH.

Primary outcomes analysis: The primary analysis will be based on an analysis of covariance (ANCOVA) to compare the improvement in liver fat due to vitamin E relative to placebo. The model will include one dummy variable for treatment group indicator as well as baseline demographic characteristics and baseline liver fat. The 95% confidence intervals for the difference between the two treatment groups will be reported.

Secondary outcomes analysis: Secondary efficacy end points are continuous and as such the ANCOVA model will be used as described for analyzing the primary outcome except that the model will include the baseline value of the response variable.