Is there a correlation between peri-operative Urinary Neutrophil Gelatinase-Associated Lipocalin (uNGAL) levels and devolvement of CKD in patients who undergo Liver Transplant?

A. Study Purpose and Rationale:

Urine Neutrophil Gelatinase Associated Lipocalin is a member of the lipocalin family of proteins, produced and secreted by numerous cells including renal tubular cells, immune cells and hepatocytes. Initially suspected to have mainly bacteriostatic activity, more recent observations have suggested that NGAL may function as a growth factor and differentiation factor in several cell types, including renal epithelia. This is supported by a massive upregulation of NGAL expression following renal tubular injury.[1] This upregulation precedes the rise of serum creatinine (sCr), and has led to a number of studies defining the role of uNGAL as an early biomarker of AKI in a number of clinical settings (Cardiac surgery, Hepatorenal Syndrome[10], Contrast Induced Nephropathy, and the glomerulonephritidies). More recently, uNGAL has been identified as a potential indicator of chronic kidney disease (CKD) progression[2].

CKD, defined as reduced glomerular filtration rate for 3 months or more, is a common complication of orthotopic liver transplantation (OLT)[3]. The KDOQI stages of kidney dysfunction are defined by the estimated GFR calculated with the Modification of Diet in Renal Disease Study equation. The data from the Scientific Registry of Transplant Recipients demonstrates the incidence of stage 4 CKD (estimated GFR <29 mL/minute) or stage 5 CKD (estimated GFR <15 mL/minute) after OLT at 1, 3, and 5 years is 8%, 14%, and 18 %, respectively[4]. The pathogenesis of CKD after OLT is multifactorial – calcineurin inhibitor (CNI) toxicity, complications of diabetes, complications of hepatitis, ischemic injury, and hypertension all potentially play a role. Pre-transplant factors associated with posttransplant kidney failure include age, pretransplant kidney disease, diabetes mellitus, and hypertension. Posttransplant factors predisposing to CKD include acute kidney injury and CNI use[4,5]. CNI-related acute renal failure is secondary to renal vasoconstriction. CKD secondary to CNIs is caused by progressive obliterative arteriolopathy and chronic interstitial fibrosis with glomerulosclerosis and develop in a dose-dependent and time-dependent fashion[6,7]. Attempts to prevent or reverse CNI-related kidney disease have been largely unsuccessful[8]**.** However, It is believed that reduction of the dose of CNIs or transition to CNI sparing regimens (mycophenolate mofetil or sirolimus) earlier may minimize renal disease progression[9].

Ultimately, sCr demonstrates renal function, rather than injury. uNGAL is a novel biomarker that identifies renal injury prior to a decrease in function. Given the mounting evidence uNGAL's ability to predict not only AKI but also progression of CKD, we hypothesize that perioperative uNGAL levels will correlate with progression of CKD after OLT.

B. Study Design and Statistical Analysis

<u>Study Design:</u>

This investigation will utilize data from 92 patients who previously underwent OLT between 2008-2009 at Columbia University Medical Campus. All of these patients were part of a study investigating the accuracy of uNGAL in predicting AKI in an intraoperative setting[11]. As such, baseline data including sCr and uNGAL were obtained at predetermined timed intervals.

All of the surviving patients continue to follow at CUMC and receive regular screening of their renal function. The objective of this prospective, observational study is to determine if there is a correlation between elevated peri-operative uNGAL levels and the development of CKD at 3, 6, 12 and 24 months post-liver transplant. Furthermore, it will be determined if this correlation changes when accounting for a number of confounders including CNI use, hypertension, diabetes, HIV, and active Hepatitis.

Statistical Analysis:

This study will utilize a linear regression to determine if there is a correlation between perioperative uNGAL and eGFR at 0, 3, 6, 12 and 24 months. Given that there are a set number of subjects of 92, in order to have a power of 80% and a P= 0.05, the smallest detectable correlation is r=±0.29.

To better assess for uNGAL's ability to predict CNI induced CKD, this same linear regression will be completed with the omission of patients with hepatitis, hypertension, HIV, and diabetes. In total, 28 patients prior to liver transplantation did not have these confounders. Similarly to have a power of 80% and a P=0.05, the smallest detectable correlation r=±0.51

C. Study Procedure:

This study will utilize data obtained from a prior study investigating the accuracy of uNGAL in predicting AKI in an intraoperative setting[11]. This included obtaining uNGAL and sCr levels pre-operatively, post-operatively, 3 hours post-procedure, 18 hours post-procedure, and 24 hours post-procedure. uNGAL was determined using a commercially available ELISA (Antibodyshop, Gentofte, Denmark) by the Irving Institute for Clinical and Translation Research of Columbia University. The limit of detection for this assay is between 0.5-4.0 pg/mL and intra-assay variation in the urine is 2.1% (range:1.3-4.0).

The monitoring of sCr post-transplant was completed as it was clinically indicated. sCR was measured by the central laboratory of Columbia University Medical Center. Typically, this is completed at monthly intervals. This data will be retrieved from the medical record retrospectively. eGFR will be determined based on the MDRD equation.

D. Study Drugs:
Not applicable to this study.

E. Medical Device:
Not applicable to this study.

F. Study Questionnaires:
Not applicable to this study.

G. Study Subjects:
This included all patients that underwent OLT from 2008-2009 at CUMC.

H. Recruitment of Subjects:

There will be no active recruitment of new patients for this study. Previous studies identified all patients undergoing OLT at Columbia University Medical Campus. The Institutional Review Board of Columbia University waived the requirement to obtain written informed consent for the collection of urine as New York State and US Federal Regulation consider this minimal risk.

All patients undergoing liver transplantation (deceased or living related) at Columbia University Medical Center were eligible for inclusion in the original study. The only exclusion criteria were patients with pre-OP renal failure requiring renal replacement therapy.

I. Confidentiality of Study Data:
Collection of patient data will be limited to only the amount necessary to achieve the objectives of the study. Password-protected and/or encrypted computers or hardware will be utilized to protect personal information. Wherever possible, patient data will be de-identified to further protect sensitive patient information.

J. Potential Conflict of Interest:

No potential conflicts of interest are identified.

K. Potential Risks:

The potential risks of this study are minimal. Currently, the only risk is the disclosure of protected health information. A number of precautions, as detailed above, will minimize this risk.

L. Potential Benefits:

As noted previously, CKD after OLT has a prevalence of up to 20% at 5 years[4]. Identifying patients that are at increased risk of CKD may allow for early implementation of renal-sparing medical treatments. This study seeks to provide evidence that uNGAL may be utilized to stratify which patients are at increased risk of CKD.

M. Alternative Therapies:

Not applicable to this study.

N. Compensation to Subjects:

No compensation will be provided.

O. Cost to Subjects:

The continued monitoring of renal function is standard of care, and thusly this study causes no additional cost to the subject.

References:

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