

Does Contrast-Enhanced
Ultrasound Positively Influence
Selection of Biopsy Sites when
Evaluating Transplant Kidneys?

NCT02625428

26 November 2014

Does Contrast-Enhanced Ultrasound Positively Influence Selection of Biopsy Sites when Evaluating Transplant Kidneys?

Protocol Date: 26 November 2014

J. Scott Kriegshauser, MD¹, Co-principal Investigator
Nirvikar Dahiya, MD¹, Co-principal Investigator
Maxwell Smith, MD²
Ray Heilman, MD³
Maitray Patel, MD¹
Scott Young, MD¹
M'hamed Temkit⁴

Introduction

Histopathological changes in kidney allograft are not always homogeneous. [1] Common pathologic abnormalities found on biopsy of transplanted organs, including renal transplants, can be patchy in distribution, especially in rejection and chronic nephropathy. [2-6] This may result in a suboptimal sample when performing a random transplant renal biopsy. [4, 6] Strategies to minimize sampling error include using larger needles or obtaining additional cores, since complications of biopsy remain very low and the benefit far exceeds the risk. [4, 6, 7] We hypothesize that contrast-enhanced ultrasound (CEUS) may help evaluate segmental differences in renal perfusion better than Doppler Ultrasound and thus help direct the biopsy to the most abnormal part of the renal cortex. This should maximize detection and increase the odds of demonstrating the true grade/severity of the histopathological abnormality.

CEUS has been FDA approved for echocardiography but its use elsewhere in the body is considered off-label. It has been used extensively outside the United States within the abdomen, but most commonly for liver masses. CEUS investigations within transplant kidneys have shown additional information can be obtained when compared to gray-scale and Doppler ultrasound. Apart from a better estimate of parenchymal perfusion it allows for evaluation of graft vascular kinetics, including quantitative measurements, e.g. time-to-peak enhancement (TTP) within the cortex or pyramids. [8-14] Studies have also shown CEUS is more sensitive to renal perfusion defects than Tc-DTPA. [15] This ability of CEUS to evaluate perfusion over time may help target renal transplant biopsies to the most abnormal segments.

Hypothesis/Expected Results

CEUS targeted biopsies to areas of decreased or inhomogeneous perfusion will show disease processes significantly more often or of a higher severity than (non-targeted) random biopsies. Additionally, this directed biopsy may demonstrate more significant or advanced disease, as measured by Banff criteria, when compared to a routine non-targeted biopsy. Random biopsies

of different segments in the same kidney, when no focal or segmental CEUS abnormality is demonstrated, will not be significantly discordant for disease or Banff criteria.

Proposed investigation

IRB approval from our institution will be obtained for this pilot study of 40 consecutive consenting male and female adult patients over 18 years of age undergoing renal transplant ultrasound-guided percutaneous biopsy within 24 months post-transplant, including patients undergoing biopsy to evaluate a recent rise in serum creatinine, so-called for cause biopsies and patients undergoing routine protocol (surveillance) biopsies without other evidence of renal dysfunction. Pregnant patients will be excluded. The routine protocol biopsies are done at 4 months and 1 year after transplant mostly looking for subclinical rejection. Informed written consent (IRB approved consent form) will be obtained from all patients prior to the scan and biopsy procedure. This will include consent for the off-label use of Optison and the need to obtain 2 or 3 biopsies specimens, when routinely only 1 or 2 are obtained. All patients will meet our standard anticoagulation guidelines for undergoing renal transplant biopsy.

CEUS will be performed in addition to our routine color-Doppler ultrasound evaluation of the transplant kidney prior to the biopsy. One vial (3.0 mL) of Optison will be utilized for each patient, with expected doses to be in the range of 1-1.5 mL for each scan sequence, allowing up to 2 to 3 scan sequences per patient exam. Low mechanical index settings and coded harmonics will be utilized. Each scan sequence will be recorded for up to 5 minutes. Post-processing will be performed using an off-line workstation if needed.

All patients will have at least 2 core biopsies of their transplant kidney under ultrasound guidance, using the cortical tangential approach whenever possible. [7] One core will be obtained from the most easily accessible location, usually the upper pole, without consideration of CEUS results (labeled “random #”, with “#” the ordinal number of the biopsy). A second core biopsy will be obtained from a segment that demonstrates variable CEUS perfusion. This sample will be labeled “targeted #”. If no abnormality is detected with CEUS, a second biopsy will still be performed in a distinctly separate location from the first (labeled “random #”). Conceivably, there could be additional biopsies added to the same “targeted #” or “random #” container if the previous biopsy in that region is/are not satisfactory or inadequate for any reason and obtained from the same general region of the kidney. We will be targeting areas of low perfusion. Many studies have shown CEUS using “global” cortical perfusion analysis can significantly aid detection of rejection (and other processes, e.g. chronic allograft nephropathy). [8, 9, 12, 14, 16] In pigs, CEUS is very good at detecting focal perfusion abnormalities. [15, 17] CEUS is better at evaluating the cortical perfusion, and not limited to segmental and interlobar artery evaluations, as with standard color-Doppler evaluations. Areas of no perfusion representing cortical infarcts would not contribute to the diagnosis and will not be targeted. The perfusion characteristics of each site based on CEUS findings will be recorded. Each will also be categorized as “For Cause” or “Surveillance”.

The order in which the randomized and targeted biopsies are performed will be randomized. Biopsies specimens sent for analysis will be labeled in order only as #1 and #2, blinded to the pathologists, with the full description (including “targeted” or “random” with the #) recorded by the performing radiologist prospectively. Each biopsy core will be evaluated separately by the pathologists. Pathologists will be as definitive as possible in making a diagnosis and specifying Banff scores for each individual biopsy core. Differences in pathology will then be reviewed and recorded as to presence of disease and differences in Banff scores.

Safety and Adverse Events

It is standard practice that patients be kept for observation 1 hour post biopsy and called by the nurse at 24 hours. Those patients participating in the study will also be called 72 hours post procedure. Any complications or adverse effects occurring within 1 week of the procedure will be recorded.

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse event Worksheet and log. The investigator will evaluate the event and determine the necessary follow-up and reporting required.

The investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

Data Handling and Statistical Analysis

All data will be entered into a secure database and anonymized. The statistician will create REDCap electronic data forms. Statistical analysis will be performed by our statistician after data has been obtained for all 40 patients. Detection rates would be compared by using the McNemar test. Based on our last 50 renal transplant biopsies, 84% were “surveillance” and 16% were “For Cause”. Positive rejection rates have been reported at 12-61% (1 month survey at MCA = 16% rejection) for the surveillance group [18-20] and 25-46% (1 month survey at MCA= 25% rejection) for the For Cause group. [20, 21] Using 12% and 25% as the baseline rate of rejection detected for Protocol and For Cause biopsies, respectively, we expect 17% of random biopsies to be positive for rejection ($0.25 \times 0.16 + 0.16 \times 0.84 = 0.17$). Conservatively, assuming a 10% false negative rate by CEUS biopsy, a sample of 40 patients has 80% power (alpha .05) if detection increases by 20 percentage points from 17% to 37%.

Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures. The investigator will ensure that the basic principles of “Good Clinical Practice,” as outlined in Title 21 of Code of Federal Regulations (CFR), Part 50, “Protection of Human Subjects”; 21 CFR, part 54, “Financial Disclosure by Clinical Investigators”; 21 CFR, part 56, “Institutional Review Boards”; and 21 CFR, Part 11, “Electronic Records, Electronic Signature,” are adhered to.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the individual obtaining consent.

Expected Deliverables

Expected time-frame, once funded, for patient recruitment and completion of procedures is 6 months, and for all deliverables is 1 year. At least 1 scientific paper or poster will be submitted for presentation at a major radiology meeting (e.g. RSNA, ARRS, or SIR annual meetings) and we will submit a paper for publication in a radiology or medical journal (e.g. Radiology, AJR, or JVIR.) All (anonymized) data will be sent to GE. Depending on results, this may serve as a nidus for a larger study.

Support Requested from GE

Provide forty vials of ultrasound contrast media (Optison). Provide post-processing quantification software for CEUS ultrasound data. Additional pathology costs, due to one additional sample for each of the 40 patients. Ten days (approximately 4% FTE) of paid radiologist “Categorical” research time. 10 hours of technologist time. Cost of statistical analysis. IRB and other fees.

¹Department of Radiology, Ultrasound Section; ²Department of Pathology; ³Department of Nephrology; ⁴Department of Biostatistics; Mayo Clinic Arizona

References

1. Piovesan, A.C., et al., *Multifocal Renal Allograft Biopsy: Impact on Therapeutic Decisions*. Transplantation Proceedings, 2008. **40**(10): p. 3397-3400.
2. Sharples, L.D., et al., *Error rates with which endomyocardial biopsy specimens are graded for rejection after cardiac transplantation*. American Journal of Cardiology, 1992. **70**(4): p. 527-30.
3. Yamataka, A., et al., *Patchy distribution of rejection changes in small intestinal transplantation*. Journal of Pediatric Surgery, 1992. **27**(5): p. 602-3.
4. Mengel, M., et al., *Protocol Biopsies in Renal Transplantation: Insights into Patient Management and Pathogenesis*. American Journal of Transplantation, 2007. **7**(3): p. 512-517.
5. Nankivell, B.J., et al., *The Natural History of Chronic Allograft Nephropathy*. New England Journal of Medicine, 2003. **349**(24): p. 2326-2333.
6. SOROF, J.M., et al., *Histopathological Concordance of Paired Renal Allograft Biopsy Cores: Effect on the Diagnosis and Management of Acute Rejection*. Transplantation, 1995. **60**(11): p. 1215-1219.
7. Patel, M.D., et al., *US-guided Renal Transplant Biopsy: Efficacy of a Cortical Tangential Approach*. Radiology, 2010. **256**(1): p. 290-296.
8. Schwenger, V., et al., *Real-Time Contrast-Enhanced Sonography of Renal Transplant Recipients Predicts Chronic Allograft Nephropathy*. American Journal of Transplantation, 2006. **6**(3): p. 609-615.
9. Łebkowska, U., et al., *Renal Parenchyma Perfusion Spectrum and Resistive Index (RI) in Ultrasound Examinations With Contrast Medium in the Early Period After Kidney Transplantation*. Transplantation Proceedings, 2009. **41**(8): p. 3024-3027.
10. Kihm, L.P., et al., *Contrast Enhanced Sonography Shows Superior Microvascular Renal Allograft Perfusion in Patients Switched From Cyclosporine A to Everolimus*. Transplantation, 2009. **88**(2): p. 261-265 10.1097/TP.0b013e3181ac8cdd.
11. Jimenez, C., et al., *Ultrasonography in kidney transplantation: values and new developments*. Transplantation Reviews, 2009. **23**(4): p. 209-213.
12. Fischer, T., et al., *Arrival time parametric imaging: a new ultrasound technique for quantifying perfusion of kidney grafts*. Ultraschall in der Medizin-European Journal of Ultrasound, 2008. **29**(04): p. 418-423.
13. Fischer, T., et al., *The use of contrast-enhanced US in renal transplant: first results and potential clinical benefit*. European Radiology Supplements, 2005. **15**(5): p. e109-e116.
14. Benozzi, L., et al., *Contrast-Enhanced Sonography in Early Kidney Graft Dysfunction*. Transplantation Proceedings, 2009. **41**(4): p. 1214-1215.
15. Stenberg, B., et al., *Post-Operative 3-Dimensional Contrast-Enhanced Ultrasound (CEUS) Versus Tc99m-DTPA in the Detection of Post-Surgical Perfusion Defects in Kidney Transplants - Preliminary Findings*. Ultraschall in der Medizin (Stuttgart, Germany : 1980), 2013.
16. Jin, Y., et al., *A Novel Simple Noninvasive Index to Predict Renal Transplant Acute Rejection by Contrast-Enhanced Ultrasonography*. Transplantation, 9000. **Online First**.
17. Taylor, G.A., et al., *Depiction of renal perfusion defects with contrast-enhanced harmonic sonography in a porcine model*. American Journal of Roentgenology, 1999. **173**(3): p. 757-760.

18. Moreso, F., et al., *Subclinical Rejection Associated with Chronic Allograft Nephropathy in Protocol Biopsies as a Risk Factor for Late Graft Loss*. American Journal of Transplantation, 2006. **6**(4): p. 747-752.
19. Nankivell, B.J., et al., *Natural History, Risk Factors, and Impact of Subclinical Rejection in Kidney Transplantation*. Transplantation, 2004. **78**(2): p. 242-249.
20. Papadimitriou, J.C., et al., *Antibody-mediated allograft rejection: morphologic spectrum and serologic correlations in surveillance and for cause biopsies*. Transplantation, 2013. **95**(1): p. 128-136.
21. Sellarés, J., et al., *Understanding the Causes of Kidney Transplant Failure: The Dominant Role of Antibody-Mediated Rejection and Nonadherence*. American Journal of Transplantation, 2012. **12**(2): p. 388-399.