Questcor Clinical Investigator Initiated Study (IIS) Proposal Guidelines

Study Title:	Use of Acthar in CKD stage V or ESRD patients in preparation for a kidney transplant
Protocol Version and Date:	4-7-15
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The italicized text is included for guidance and should be deleted from final document. Kindly complete the following information, there is no limit as to how much information to provide.

Please submit by email this completed IIS Proposal along with your ***curriculum vitae*** to your MSL.

A. SPECIFIC AIMS

Please provide a concise summary of the overall project (a few sentences) and briefly describe each Specific Aim, and include hypotheses for each endpoint (see Section C).

The specific aim of this study is to determine the rate of recurrent FSGS through evaluation of kidney biopsies performed post renal transplantation.

The primary end-point is to measure proteinuria prior (if patient still makes urine) and after renal transplantation and determine the change in proteinuria and the recurrence of FSGS as seen in kidney transplant biopsy. Kidney transplant biopsies will be performed at time O (at implantation), 3 months and 12 months post transplantation.
Our hypothesis is that the use of acthar, on patients with history of FSGS as cause of chronic kidney disease, prior to renal transplantation decreases the probabilities of patients developing recurrent disease after renal transplantation.
Secondary end point is to evaluate renal function after transplantation as measured by eGFR. We hypothesize that patients will maintain a stable eGFR and creatinine while on acthar and after it is stopped.

B. BACKGROUND AND CLINICAL SIGNIFICANCE

Wait time for kidney transplantation is on average at least 5 years and unfortunately many patients die while waiting for kidney transplantation. Recurrent disease affects 23% of renal transplant recipients with FSGS. No known genetic mutations have been identified among those with recurrence. Plasmapheresis has resulted in complete or partial remission in 75% of those with recurrence after transplant but this treatment is very aggressive as it increases bleeding risk and involves the placement of a catheter. Furthermore, it is performed usually three times a week for months in order to achieve remission. Modern immunosuppression does not reduce the rate of recurrent FSGS (1).

Typically, recurrence of primary FSGS occurs early in the post transplantation period with heavy proteinuria and progressive renal insufficiency and graft failure. Current animal and human data suggest that primary FSGS is likely to be initiated by podocyte injury; however, Savin *et al.* (2) described a circulating plasma factor and its association with many cases of primary and recurrent FSGS. The rapid nature of recurrent FSGS after transplantation is consistent with the theory that one or more circulating factors may be playing a major role in the pathogenesis of recurrence (3).

Acthar is FDA approved for the treatment of nephrotic syndrome. It still has not been studied in renal transplant patients, but clinical data in our center has been very encouraging and it has been used safely and effectively in renal transplant recipients with FSGS.

Recent data has shown an etiologic role of perturbations of the CD40 antigen in recurrent FSGS[1]. It is unknown if acthar would change CD40 in patients with FSGS. As part of our research investigation, we propose to investigate CD40 in kidney biopsies, by immunohistochemistry, and serum of patients, by ELISA. Patients will have one pre-transplant serum sample which will be measured for CD40 by utilizing the CD40 antibody through ELISA. A 2nd blood sample will be obtained at 3 months post transplant, at 6 months post transplant and at 1 year post transplant. This blood will be drawn with standard of care labs, so it would not impose additional blood draws to the patient.

C. RESEARCH DESIGN AND METHODS

Study Type/Design

Prospective study enrolling renal transplant recipients with the primary native kidney disease of FSGS.

Endpoints *primary and secondary*

Primary endpoint is rate of recurrence of FSGS as seen in renal transplant biopsies and in rate of proteinuria

Secondary endpoint is renal function after transplantation

Patient Recruitment *Subject number, target population, Inclusion and Exclusion criteria*

The target subject number is 20 patients and the target population is primary FSGS patients. By the current data, FSGS should recur in 23% of patients. Therefore, it would be expected that at least 4 patients will develop recurrent FSGS after renal transplantation.

Exclusion criteria will include patients whose primary disease is not FSGS, patients who are receiving dual organ transplants and patients who have been on acthar prior to transplantation.

Treatment Overview *Screening protocol, concomitant treatments, etc.*

Screening will be performed by the Principal Investigator during the kidney transplant evaluation clinics and during the wait list kidney transplant evaluation clinic. All patients with FSGS will have maintenance

immunosupression with belatacept (if EBV negative), prograf, cellcept and prednisone. If after one year the patient has been stable and there has not been rejection, will stop the prograf and continue solely with belatacept, cellcept and prednisone.

Dosage and Administration of Acthar

The dose of acthar to be given to every enrolled patient will be 80 units twice a week for 6 months.

Laboratory Testing and Study Schedule

Patients will have one pre-transplant serum sample which will be measured for CD40 Ab. A 2nd blood sample will be obtained at 3 months post transplant, 6 months post transplant and at 1 year post transplant. This blood will be drawn with standard of care labs, so it would not impose additional blood draws to the patient.

- The first month post transplant, patients will have labs and clinic visit biweekly.
- The second month post transplant patients will have labs and clinic visit weekly.
- The third month post transplant patient will have labs weekly and clinic visit every other week.
- From the 4th till the 6th month post transplant patients will have labs every other week and clinic visit monthly.
- From month 6 till month 12 patients will have labs monthly and clinic visit every other month.

Patient Monitoring and Evaluation *Contingencies for patients not responding (i.e. dose adjustment, schedule change)*

Patients will have a kidney biopsy at time 0 (at the time of implantation), 3 months and 12 months. If at any other time it is clinically necessary to perform another biopsy it will be performed. Any extra kidney transplant tissue will be used to stain for CD40 Ab. This would not impose an extra risk as it will be part of the standard of care kidney transplant biopsy.

Potential Pitfalls and Contingencies *Describe plans to address possible problems*

We will ideally attempt to avoid plasmapheresis after renal transplantation, but if a patient develops severe proteinuria will start plasmapheresis and monitor proteinuria until it decreases. If there is no change in proteinuria after a month on plasmapheresis, will stop plasmapheresis and continue only with acthar.

Data Processing and Analysis

Statistical /Analytical Plan *Include data management and quality assurance*

All patient information will be de-identified for study purposes.

Sample Size Justification *Include power analyses or justification for enrollment plan*

This is a pilot study to determine if acthar helps decrease the rate of recurrent FSGS after renal transplantation.

D. REGULATORY, SAFETY AND MONITORING

Describe the plan for subject follow-up, safety reporting, removal of subjects from study, etc. Please also indicate that an IND will be filed with the FDA prior to study start and that investigator/sponsor will comply with US Public Law 110-85 which mandates for ClinicalTrials.gov registration and reporting, if applicable. (The IIS research agreement will stipulate notification to Questcor of all Adverse Events.)

There will be a committee composed of 3 member and we will monitor the data and safety measures periodically. We will monitor AEs on a weekly basus. One of the committee members will be unbiased to the study.

E. ESTIMATED DURATION OF THE STUDY AND CRITICAL TIMELINE ELEMENTS

I. Please complete expected/estimated dates:

Table 1: Critical Timeline Elements	
Element Name	**Date**
IRB approval, expected	IRB Submission: 6/1/2015 IRB Meeting Date: 6/18/2015 IRB Approval Date: Mid- Late June 2015
IND submission, expected	IND Submission: 6/1/2015
Study start date, estimated	June 30 2015
Enrollment completion date, estimated	June 30 2018
Study completion date, estimated	June 30 2019

II. Describe publication plan and anticipated number of abstracts and manuscript submissions (include intended conference(s) for presentation and month, year of conference(s)):

Plan is to have an abstract submitted for a large meeting, such as the American Transplant Congress, the American Society of Nephrology Meeting or the World Transplant Congress by January 2017. Interim paper publication should be done by the fall of 2017 and full paper publication by the summer of 2019.

F. REFERENCES

1. Recurrent focal segmental glomerulosclerosis in the renal allograft: single center experience in the era of modern immunosuppression. Schachter ME[1], Monahan M, Radhakrishnan J, Crew J, Pollak M, Ratner L, Valeri AM, Stokes MB, Appel GB. Clin Nephrol. 2010 Sep;74(3):173-81.

2. Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis. Savin VJ, Sharma R, Sharma M, McCarthy ET, Swan SK, Ellis E, Lovell H, Warady B, Gunwar S, Chonko AM, Artero M, Vincenti F. N Engl J Med334 :878– 883,1996.

3. Recurrent glomerulonephritis after renal transplantation: an unsolved problem. Golgert WA[1], Appel GB, Hariharan S.Clin J Am Soc Nephrol. 2008 May;3(3):800-7. Epub 2008 Feb 13.