The Use of Acthar (ACTH) in Patients with Focal Segmental Glomerulosclerosis (FSGS) Who Have Developed Chronic Kidney Disease Stage V (CKD) or End Stage Renal Disease (ESRD) and Are Undergoing a Renal Transplant

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I.Hypotheses and Specific Aims

This is an open-label pilot study where all subjects will be treated with the drug, Acthar. The specific aim is to determine the rate of recurrent FSGS through evaluation of kidney biopsies performed post renal transplantation. FSGS is a type of nephrotic syndrome that can recur aggressively after renal transplantation. When FSGS recurs after transplant it increases patient morbidity and increases graft loss.

It is believed that ACTH, besides steroid dependent properties, has steroid independent properties (see figure 1 on page 10). With the steroid independent properties it may stimulate the MCIR receptor which affects not only the podocytes, but also the T-cells, B-cells, NKR-cells and APC-cells.

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, at the time of renal transplantation and for a 6-month period of time following transplant, decreases the probabilities of patients developing recurrent disease after renal transplantation.

Our 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.

II. Background and 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 23-30% 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). Moreover, recurrence after transplantation, where the patient is already immunosuppressed, is a poor prognostic factor and it brings a high risk of graft failure.

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. The FDA package insert of Acthar: “To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematous.” (3). 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.

This medication has been studied in nephrotic syndrome in native kidney disease. Most studies have used a dose of 80 units twice a week (one cc of the medication contains 80 units). There is no data on the renal transplant population, but is interesting to note that with the steroid independent properties, Acthar may target several cell linages that are relevant in transplantation and maybe a reason of why this medication can work to decrease recurrence after transplantation.

Recent data has shown an etiologic role of perturbations of the CD40 antigen in recurrent FSGS (4). 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.

We expect from 7-10 patients a year to meet inclusion criteria.

III. Research Methods and Design

A. Study Type/Design:

Prospective open-label study enrolling renal transplant recipients with the primary native kidney disease of FSGS. This protocol already has an IND exemption as this medication is FDA approved for the treatment of nephrotic syndrome. All subjects will receive Acthar.

B. Endpoints

The primary endpoint is rate of recurrence of FSGS as seen in renal transplant biopsies and in rate of proteinuria.

The secondary endpoints are duration of remission after Acthar treatment (Time Frame: 1 year and 2 years of study follow-up after treatment completion), changes in kidney fibrosis after Acthar treatment and safety and efficacy of Acthar in the post renal transplant population.

C. Patient Recruitment

Preliminary data was previously submitted in the American Transplant Congress 2017. Post renal transplant recipients that developed FSGS were treated with Acthar at the discretion of the investigator. Half of the patients experienced reductions in proteinuria. Prior to the introduction of this medication, developing recurrent FSGS in the renal transplant meant that the renal transplant would likely be lost within a year.

This is a single center pilot study where the target subject number is 20 patients and the target population is primary FSGS patients. By the current data, FSGS should recur in 23-30% of patients. Therefore, it would be expected that at least 4 patients will develop recurrent FSGS after renal transplantation.

After we obtained data from this pilot study we would expect to request funding for a large multicenter study.

Inclusion Criteria:

1. Adult renal transplant recipients with primary FSGS
2. Ability to consent

Exclusion Criteria:

1. Renal transplant recipients whose primary disease is not FSGS

2. Patients who are receiving dual organ transplants
3. Patients who have been on Acthar prior to transplantation.
4. Intractable CHF (congestive heart failure)
5. Uncontrolled hypertension definied as BP >180/100
6. Uncontrolled diabetes defined as a HgbA1c>10%
7. An acute infection
8. Allergies to pig-derived proteins
9. Have received a live vaccine three months prior to transplant
10. Cushing's syndrome
11. Addison's disease
12. Previous intolerance to native ACTH or proteins of porcine origin
13. History of scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of peptic ulcer, primary adrenocortical insufficiency or adrenocortical hyperfunction.
14. Recent cardiovascular event within 3 months of screening including: Myocardial Infarction, CVA, TIA, New York Heart Association Functional Class III or IV failure, Obstructive valvular heart disease, or hypertrophic cardiomyopathy, second or third degree atrioventricular block not successfully treated with a pacemaker.
15. History of HIV
16. New diagnosis of cancer or recurrent cancer within 2 years of screening
17. History of alcohol or drug abuse within 12 months of study entry.
18. Receipt of any investigational drug within 30 days of enrollment.
19. Psychiatric disorder that interferes with the patient's ability to comply with the protocol.
20. Poorly controlled diabetes with an HbA1C > 10%
21. Type 1 diabetes mellitus
22. Pregnancy

D. **Treatment Overview**

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 induction therapy with thymoglobulin and maintenance immunosuppression with tacrolimus and mycophenolate. This is the standard regimen that we utilize post transplant in all our recipients.

E. **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. The first dose of Acthar is given at the time of transplantation and will be continued, twice a week, for 6 months. See Appendix A (page 9) for additional details.

Safety:

1. Acthar should always be injected beneath the skin or into the muscle.
2. Never inject Acthar directly into a vein.

Risks:

1. Development of high blood sugars (10%)
2. Development of high blood pressure (11%)
3. Edema (1%)
4. Mood and behavior changes (7%)
5. Weight and appetite changes (1%)

We will be monitoring all patients at the stated time points for all the above risks and side effects. We will be monitoring side effects with our research transplant coordinator and the PI who will be seeing the patients. We will also have a safety officer, Dr.Jessica Kendrick, who will be reviewing the adverse events. At every clinic visit, as standard of care, patients get their vital signs taken as well as urinalysis and laboratories. We will be reviewing all the results carefully and assess every patient to see if there are any signs of infection. Dr.Kendrick will also be part of the DSMB. While Dr. Kendrick will review safety date and adverse events every three months, the DSMB, of which she will be a member, will meet every 12 months.

F. 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.
Standard of care labs include CBC, BMP, tacrolimus level, BK PCR plasma, CMV PCR plasma, DSA, Allosure testing and urine protein/creatinine.

- 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.

Dr.Joshua Thruman, a nephrologist and immunologist, will be helping in the testing of CD40 Ab. ELISA will be used in patient's serum to test for CD40. In addition, human kidney biopsy tissues will be fixed in formalin or AFA (alcohol–formalin–acetic acid) solution and embedded in paraffin. For CD40, antigen retrieval was performed by proteinase K digestion and then hydrolysis by heating in a microwave oven with citrate buffer. The rabbit polyclonal primary anti-CD40 Ab (Anti-CD40 Ab 11E9, Abcam) will be diluted at 1:150 and incubated overnight at +4°C. A three-step technique will be used with biotinylated anti-rabbit secondary Ab, avidin-biotin-peroxidase complex as the vector, and 3,3′-diaminobenzidine (DAB) as the substrate.

G. Patient Monitoring and Evaluation

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. We will be collecting clinical data from the patient's medical record including medications, CBC, CMP, urine protein/creatinine, BK, CMV, adverse events, infections and any hospital admissions.

H. Potential Pitfalls and Contingencies

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, we will stop plasmapheresis and continue only with Acthar.

I. Specific participant and study stopping criteria:
1. Development of severe hypertension definied as BP > 180/100
2. Development of congestive heart failure
3. Severe edema that is impeding ability to breath
4. Withdrawal of consent
5. Pregnancy
6. Use of immunosuppressive drugs other than those specified by the protocol except those needed to treat FSGS and proteinuria
7. Any other protocol deviation that results in significant risk to the patient's safety.

J. Data Processing and Analysis

Sample size: A sample size of 20 data pairs (for example from immediately post-transplant to 12 months post-transplant) achieves 80% power to detect an effect size of change in proteinuria of 0.66 standard deviations with a significance level (alpha) of 0.05 using a two-sided paired t-test. A sample size of 20 produces an exact two-sided 95% confidence interval from 0.087 to 0.491 when the recurrent FSGS proportion is 0.25, i.e. 5/20 patients. If only 4/20 patients develop recurrent FSGS the 95% confidence interval would be 0.057 to 0.437 and if 3/20 patients developed FSGS the 95% confidence interval would be 0.032 to 0.379. This lack of precision in the estimate of the proportion of patients developing recurrent FSGS is due to the small sample size. However, this is a pilot study to determine whether Acthar helps decrease the rate of recurrent FSGS after renal transplantation. The observed rate of recurrent FSGS in patients treated with Acthar will be used to power larger, multicenter studies. We will seek expert opinion from the participating centers regarding expected rates when planning the trial. The outcomes which will be used to plan for a future, larger, more definitive trial will include recurrent FSGS as observed in this pilot study as well as change in proteinuria over time.

Data analysis: Data will be analyzed using two-sided paired t-tests for comparing two time points as well as mixed effects models for multiple time points, to assess changes in proteinuria over time. Other clinical, pathological and laboratory variables may be included in the models to determine whether the change over time is affected by these covariates. Similar methods will be used to model changes in eGFR over time. The observed proportion of patients developing recurrent FSGS will be reported as a proportion with an exact 95% confidence interval. Standard of care labs including CBC, BMP, tacrolimus level, BK PCR plasma, CMV PCR plasma, DSA, Allosure testing and urine protein/creatinine as well as biopsy findings will be reported as summary statistics (means ± SD, medians (with interquartile range) and proportions as appropriate) at each time point.

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

We will monitor the data and safety measures periodically. We will monitor AEs on a weekly basis.

Our 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.

K. Designation of Independent Monitor:

The PI will designate an Independent Monitor to perform an independent review of ongoing study progress and safety. The Independent Monitor should not be involved with the study or work with the PI, although he/she could work within the same institution. The Independent Monitor for this study is Dr. Jessica Kendrick. Dr. Kendrick is not associated with this research project and thus works independently of the PI, Dr. Monica Grafals. Dr. Kendrick is not a part of the key personnel involved in this grant, and is qualified to review the patient safety data generated by this study because of her unique expertise in the area of the nephrology. Dr. Kendrick's CV is attached. Dr.Kendrick will be in the DSMB. She will review safety date every 3 months and then meet formally as a DSMB every 12 months.

IV. 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. Acthar Full Prescribing Information

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

Appendix A – Acthar (ACTH) Study Visit Schedule

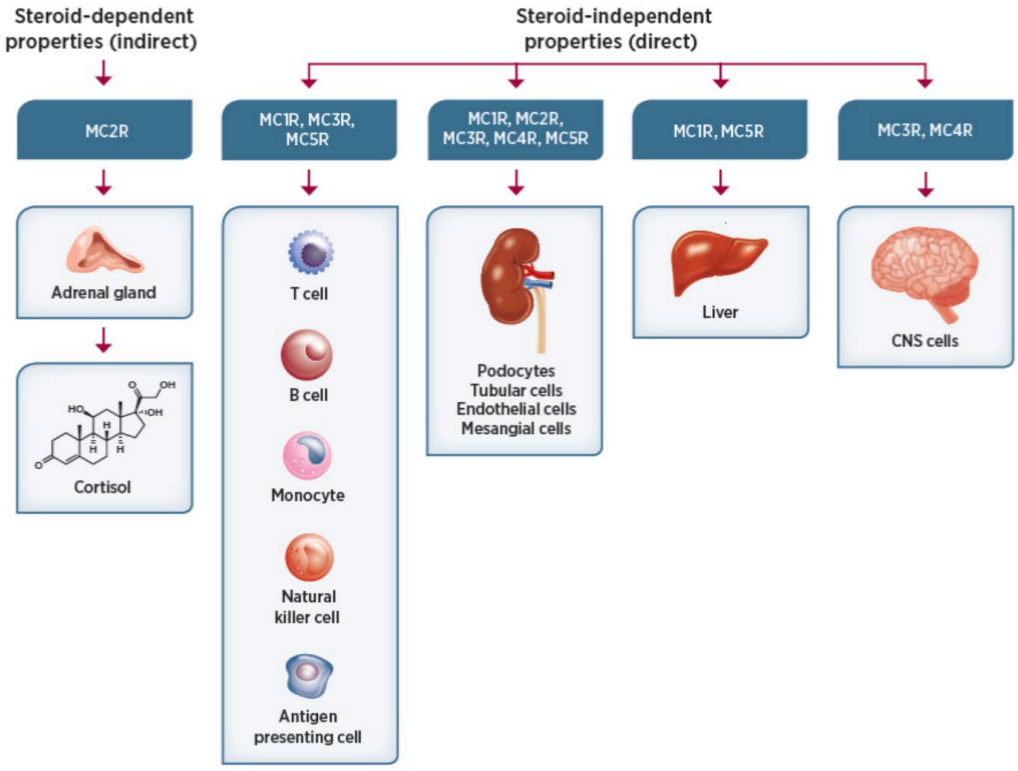
	SCR	OR	Day								Week				Month												
	-21- 0	0	4	7	10	14	18	21	25	28	5	6	7	8	3	4	5	6	7	8	9	10	11	12	18	30
Informed consent	x																									
Background information	x																									
Inclusion/exclusion	x																									
Medical History	x																									
Transplant information		x																								
Pregnancy test	x																									
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x		x		
Physical exam	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x		x		
Laboratory tests *[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Renal Biopsy		x													x									x		
Study medication *[2]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x								
CD40 Ab *[3]	X														X			X					X		
Follow-up (for secondary data on remission: yes or no)																									X	X

*1 All laboratories (except CD40 Ab – see footnote *3) are part of SOC/Standard of Care. SOC labs include CBC, BMP, tacrolimus level, BK PCR plasma, CMV PCR plasma, DSA, Allosure and urine protein/creatinine.

*2 Study medication (Acthar) will continue twice a week through month 6 post-transplant.

*3 CD40 Ab which will be measured pre transplant, at 3, 6 and 12 months. This laboratory will be drawn at the same time as SOC labs so that patient does not have an additional blood drawn. Dr. Josh Thurman will assist with the testing of the CD40 Ab.

Figure 1


Steroid-dependent properties (indirect)
Steroid-independent properties (direct)
MC2R
MC1R, MC3R, MC5R
MC1R, MC2R, MC3R, MC4R, MC5R
MC1R, MC5R
MC3R, MC4R
Adrenal gland
Cortisol
T cell
B cell
Monocyte
Natural killer cell
Antigen presenting cell
Podocytes
Tubular cells
Endothelial cells
Mesangial cells
Liver
CNS cells