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Official Title: Treatment of Chronic Antibody-mediated Rejection in Kidney Transplant with Acthar

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Questcor Clinical Investigator Initiated Study (IIS) Proposal Guidelines

Study Title:	Treatment of Chronic Antibody-mediated Rejection in Kidney Transplant with Acthar
Protocol Version and Date:	
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A. SPECIFIC AIMS

Use of Acthar for treatment of chronic antibody-mediated rejection in kidney transplant recipients is safe and associated with improved graft outcome

B. BACKGROUND AND CLINICAL SIGNIFICANCE

Chronic antibody-mediated rejection (CAMR) is the clinico-pathological manifestation of chronic active graft injury as a result of donor-directed antibody. This type of graft injury is the major cuase of graft faliure after the first year of transplantation. The dominant histological manifestation of this process is transplant glomerulopathy (TG), characterized by double contours in more than 10% of glomerular capillary loops. Gloor JM et al observed that among indication and protocol biopsies, 9.5% of the patients had TG at a median of 21±14 months (range 4-61) after transplant. It could also present as peritubular capillary basement membrane multilayering, interstitial fibrosis/tubular atrophy, and/or fibrous intimal thickening in arteries. CAMR is strongly and independently associated with poor graft survival. In the study by Gloor et al, mean graft survival after the diagnosis of TG was 43±7 months. We examined the outcome in 145 patients with TG at our center (unpublished data). Graft survival at 66 months of diagnosis was only 10%. The role of donor-specific alloantibody (DSA) in pathogenesis of graft injury in CAMR has been clearly demonstrated. Through complement dependent and independent mechanisms, the antibodies cause phenotypic changes in endothelial cells (EC). Inflow of inflammatory cells, especially monocytes ensue, and with ongoing EC injury, diminished patency of the capillary loops and progression to reduplication of the glomerular basement membrane occurs. Our group has shown the strong association of glomerular CD 68-positive cells. (macrophages) with TG, and as the only independent predictor of graft survival. The clinical manifestation of CAMR is generally insidious and non-specific, consisting of proteinuria, unexplained loss of allograft function, and hypertension. Unfortunately, there is no specific therapeutic regimen for this major cause of graft failure. The role of Melanocyte stimulating hormone (MSH) receptors in suppressing inflammation through downregulation of the lymphocytes, macrophages, PMNs and eosinophils, and their role in protecting the glomerular endothelial cells and podocytes, provide a strong rationale for use of Acthar in treatment of CAMR. We have hypothesized that Acthar therapy in patients with CAMR is safe and delays the resultant graft injury. We propose to conduct an open-label, uncontrolled, pilot prospective cohort study using Acthar as a part of immunosuppressive regimen for patients with clinical/histological diagnosis of CAMR.

C. RESEARCH DESIGN AND METHODS

Study Type/Design

This is an open label safety and feasibility trial using Acthar® in addition to our center-specific standard therapy, which could include increase in maintenance immunosuppression, high dose IVIG (2 g/Kg), and/or Rituximab, in patients with CAMR.

The **inclusion criteria** include:

- Age >18 years
- Morphologic diagnosis of CAMR, by light &/or electron microscopy any time after transplantation
- eGFR>25 ml/min

The **exclusion criteria** include:

- Diagnosis of malignancy within a year prior to enrollment (except cured cutaneous basal cell or squamous cell carcinoma).
- Lack of evidence of antibody involvement
- Pregnancy, lactation, or refusal to use birth control in women of child bearing potential
- Active infection, or history of HIV
- History of liver or thoracic transplant

Endpoints

The **efficacy primary endpoint** of the study is the composite of graft loss, death, decrease in eGFR>10%, and increase in proteinuria, defined by >50% increase if baseline proteinuria <2 g, or persistence of proteinuria >2 g otherwise, at one year after initiation of the treatment. The **safety endpoints** include the serious adverse events during the study period attributable to study drug.

Secondary end-points:

1- Death
2- Graft loss (defined as return to dialysis or retransplantation)
3- Decrease in eGFR>10% at 1 year
4- Increase in proteinuria >50% if baseline proteinuria<2 g, or persistence of proteinuria >2 g otherwise
5- Persistance of DSA, by number of antibodies and related MFI
6- g and cg scores in the biopsies, maximum number of glomerular CD68+ cells; severity of interstitial fibrosis/tubular atrophy

Patient Recruitment

The study will be conducted in renal transplant recipients with histological diagnosis of chronic AMR at any time after transplantation with fairly preserved graft function. We are planning to enroll 20 patients with histological diagnosis of CAMR.

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

Dosage and Administration of Acthar

Subjects will receive Acthar® 40 units twice a week subcutaneously for 2 weeks. If the drug is well tolerated the dose will be increased to 80 units twice a week for another 22 weeks.

Dosage considerations in special circumstances, and based on

the side effect profile of individual participants, the investigator may recommend a

modified dose Acthar® as indicated below:

1) Patients with diabetes may be given Acthar® 16 units daily, instead of 80 units twice a week (with the aim of maintaining better glycemic control (Tumlin 2013)
2) Patients who develop side effects on the standard dose of Acthar® (40 units twice a week followed by 80 units twice a week) may be given a lower, tolerable dose of Acthar® either on a daily or a twice a week basis.

The patients will be maintained on their center-specific standard maintenance regimen, typically consisting of Tacrolimus,

Mycephenolate Mofetil/Sodium, and prednisone.

Patient Monitoring and Evaluation /Laboratory Testing and Study Schedule

After screening for the inclusion/exclusion criteria, the patients will be consented and enrolled in the study. The initial visit and subsequent study-related visits at 2, 4, 8, 12, 24, 36 and 52 weeks will include routine evaluation and physical examination and laboratory studies including CBC, electrolyte panel, eGFR, albumin, liver enzymes, and CNI/Sirulimus drug level, according to the center's standard of care. DSA will be tested at week 24, and 52 and patients will undergo a biopsy at week 52, as a part of our standard of care. The biopsies will be evaluated by light and electron microscopy using standard histological Banff criteria, and staining for CD68.

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

We do not expect major problems with the treatment. It is not clear if treatment with Acthar will prevent or slow down the progression of CAMR. However, since there is no alternative therapy available, lack of response will not change the course of the disease process. There is a possibility that the patients could develop hyperglycemia; if so appropriate therapy will be provided.

Data Processing and Analysis

Statistical /Analytical Plan

The data will be collected on the variables listed above. Standard statistical methods will be used for description of primary and secondary endpoints. As a secondary analysis a historical cohort of patients with CAMR will be identified and graft survival in the study group will be compared with the historical cohort using survival analysis methods.

Sample Size Justification

The enrollment plan is not based on power calculation, as there is no previously successful treatment reported to use for sample size calculation. This is a cohort of reasonable size that is expected to provide invaluable data regarding the treatment effect, and provide data for power calculation for future studies.

D. REGULATORY, SAFETY AND MONITORING

After the initial visit the subsequent study-related visits will occur at 2, 4, 8, 12, 24, 36 and 52 weeks and will include routine evaluation and physical examination and laboratory studies as noted above for evaluation for efficacy and safety endpoints. The adverse effects will be reported to IRB and the sponsor, and patients with serious adverse effects resulting from the study drug, not amenable to medical therapy and those non-compliant with study protocol will be removed from the study. IND will be file with the FDA if the IRB requires it. The study protocol will be registered with Clinical trials.com

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	4-6 weeks
IND submission, expected	6 weeks
Study start date, estimated	April 1, 2015
Enrollment completion date, estimated	December 31, 2020
Study completion date, estimated	December 31, 2021

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

At one year and 2 years the interim analysis will be performed and the results will be submitted to national/international nephrology/transplant meetings, and at the completion of the study the final results will be submitted in the form of a primary manuscript reporting the primary efficacy and safety data, and secondary manuscripts reporting different secondary endpoints, as appropriate. .

F. REFERENCES

R Ugarte, B. Kiangkitiwan, A. Haririan. Antibody-mediated rejection in kidney transplantation. 2014. 281-300. In M. Weir, E. Lerma (editors): Kidney Transplantation, Practical Guide to Management. Springer

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