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TITLE: Preemptive Rituximab to Prevent Recurrent Focal Segmental Glomerulosclerosis Post-Transplant

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CONTRACTING ORGANIZATION: University of Minnesota, Minneapolis, MN

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14. ABSTRACT Focal segmental Glomerulosclerosis (FSGS) is a progressive chronic kidney disease that accounts for 4% of adults and 12% of children with end-stage kidney disease in the US. Kidney transplantation is the preferred treatment for end-stage kidney disease, however FSG can recur post-transplant in 30-50% of these patients, leading to poor graft survival. Treatment options for recurrent FSGS have included plasmapheresis or rituximab, neither of which are curative or effective in all patients. Recently, prophylactic approaches have been pursued as potential means to improve outcomes. Rituximab, an agent shown effective in the treatment of some patients with FSGS, prevented recurrence in a handful of high risk transplant patients. However, the role of pre-emptive treatment with rituximab combined with plasmapheresis in prevention of FSGS recurrence is unknown, necessitating a randomized controlled trial of this pre-transplant therapy plan.								
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1. INTRODUCTION:

This is a phase III, multicenter, randomized, open-label, clinical trial to test the hypothesis that plasmapheresis plus rituximab prior to kidney transplantation can prevent recurrent FSGS in children and adults. In addition, this study will collect DNA from patients treated in this study as well as prevalent patients with FSGS who have received a kidney transplant in order to identify genetic risk factors for recurrence.

2. KEYWORDS:

Kidney disease, Focal Segmental Glomerulosclerosis, FSGS, kidney transplant.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1: Clinical trial preparation and start up

1. Hire and train project manager/coordinator for UMN, Month 1-2, Thu Danh, MPH hired 7/9/18, Training completed 7/15/18
2. Refine eligibility criteria, exclusion criteria, screening protocol, Month 1-2, Complete 10/12/18
3. Finalize consent forms, human subjects protocol and CRFs and submit to UMN IRB, Month 1-2, Submitted to UMN IRB on 10/12/18, Reviewed by IRB 11/26/18 with requested changes, Resubmitted 12/7/18, Scheduled for IRB review 1/7/19. Received UMN IRB approval 1/18/2019.
4. Finalize statistical analysis plan, Month 1-2: Started, not complete. Expected completion Q1 2021.
5. Finalize clinical trial budget and clinical trial agreement (CTA) template for additional sites, Month 1-2: Complete 6/26/18
6. Coordinate with Sites for clinical trial agreements (CTAs), Month 2-6; 17 sites sent invitations, 20 sites confirmed participation and returned preliminary documents, 0 sites have completed subawards, 1 site will not be participating, 1 new site invited to participate. Subawards sent to sites 9/2019. 15 sites have agreed to participate and have completed CTAs, 9/1/2021.
7. Coordinate with Sites for material transfer agreements (MTAs) for DNA to be sent to Duke, Month 2-6: Completed. MTAs sent to sites 9/4/19. UMN MTA complete 9/10/19.
8. Time required for submission and exemption of an Investigational New Drug (IND) application to the U.S. Food and Drug Administration, Month 1-6, Complete 11/21/2017 Received "study may proceed" notification from FDA, IND #137324
9. REDCap database design and build, Month 1-6; Changed electronic data management system to OnCore to be in compliance with reporting and data security. CRFs and randomization functions built. Complete.
10. Submit to DoD Human Research Protections Office- Submitted on 3/11/2019. Received DoD approval 08/29/2019 to start enrollment for UMN site.
11. As of 9/29/2020, the study has 13 sites that have local IRB approval and 9 of those sites have DoD approval. Nine sites are open for accrual. As of 9/30/2021, 15 sites have local IRB approval and 14 of those sites have DoD approval. Sites maintain continuing review throughout the project.

Major Task 2: Clinical trial

1. Initial Training of Site Coordinators and study staff, 6-9 months. On-going due to staff changes.

Major Task 3: Monitoring

1. Invite DSMB members to participate and receive commitments, Month 2-6, Completed 9/30/18. DSMB will be composed of Ty Dunn, MD (Adult transplant surgeon, chair), Michael Somers, MD (Pediatric nephrologist), David Nelson, PhD (Statistician).
2. DSMB members convened on 8/2/2019 to go over the PRIVENT FSGS project and roles and responsibilities of members. Approved Charter of DSMB.
3. DSMB convened on 11/18/2020 to review the status of the trial. They deemed that the study was safe to continue.

What was accomplished under these goals?

1) Major Activities: The third year of the grant have been dedicated to completing the start-up process which has been completed. 14 participating sites have been opened for accrual. Some sites are slowly screening and recruiting participants but due to Covid-19, recruitment has been difficult. The project was suspending for 4 months during the initial pandemic. With the setback, the project has randomized 4 patients and are awaiting to randomize another patient once transplantation date is known. Two patients are in the treatment arm of the study and the other two are in the control arm. The study team have also been recruiting for Aim 2 of the project which is to collect DNA samples of prevalent FSGS cases. The study has collected 27 samples.

Due to low enrollment, the study team has been discussing ways to improve recruitment. An investigators' meeting was held to determine barriers of recruitment. The study team is working with participating sites to address these issues.

As of 9/30/2021, the project has 14 sites that are opened for accrual. The study had one site, University of Maryland that is no longer participating as of June 8th, 2021. This was reported to HRPO of DoD and received on June 14th, 2021.

The study also updated the inclusion criteria to help with recruitment of potential patients. After discussions with investigators, the study increase the age of eligibility up to 65 years of age. The study initially had age of eligibility up to 45 years of age. The study also revised the number of transplantation to up to three if patients met the other inclusion criteria. The changes to the inclusion criteria was approved by local IRB and sent to HRPO who deemed the changes minimal. The updated inclusion was sent to all participating sites who then submitted to their local IRB for approval as well.

2) Specific Objectives: The project currently has 14 sites opened for accrual as of 9/30/2021. Specific objective for this reporting period was to complete approval of sites and have them ready to screen and recruit. The study team is working with one more site to get approval from HRPO.

3) Significant Events: The Covid-19 pandemic continues to affect the project in terms of enrollment. With the project placed on hold for 4 months, it has caused delays in the timeline. Sites had to get approval of Sunrise Plans to ensure the safety of research staff and patients. Many sites had to divert resources to Covid-19 and Covid-19 projects.

4) Other Achievements: Nothing to report.

What opportunities for training and professional development has the project provided?

Study staff were given one-on-one training with technical experts on the data collection tool that is being used, OnCore. The study team have conducted monthly calls for study coordinators to ask questions and voice any concerns. The team has also provided video trainings on the data collection tool for coordinators to review when needed. OnCore training is an ongoing tool that is provided to the research coordinators.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

The study team plan to continue to enroll patients for Aim 1 and Aim 2 of the PRIVENT FSGS project. The main goal of the study is to increase screening and enrollment numbers particularly for Aim 1. The study team with the help of the investigators from the different sites will discuss and create an action plan on ways to increase enrollments. All but one site are opened for accrual and the objective of the participating sites is to recruit and enroll qualified patients.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

5. CHANGES/PROBLEMS:

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

The pandemic has affected the project by delaying it and continues to affect the project with recruitment and enrollment. The study team has also noticed the difficulty of enrollment of the project due to multiple reasons. Many potential patients and patients' parents are opting out of the research project because of trust issues, not aligning with study procedures, and overall disinterest. The project has encountered that some participating sites do not have the bandwidth to carry out the study procedures such as issues with plasmapheresis or low rates of FSGS. The study team have had meetings with investigators to brainstorm ideas and create a plan to address these problems. The study team will continue to screen and recruit patients as well as seek a no-cost extension for the project. The study team has also set up a meeting with the project officer at DoD for guidance.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Michelle Rheault, MD

Co-PI

ORCID # 0000-0003-2494-3970

2 months

Dr. Rheault has provided oversight of IRB submission as well as DOD submission and contracting with additional sites. She has had oversight of the OnCore database build. She continues to be the primary person in contact with DoD and has complete oversight of the project.

Priya Verghese, MD, MPH

Co-PI

ORCID # 0000-0002-8836-0881

2 months

Dr. Verghese has recruited and managed the multi-site aspect of the project. She leads the team in developing recruitment strategies and site activation.

Thu Danh, MPH

Study Project Coordinator

ORCID # 0000-0001-7287-9980

12 months

Thu has worked with obtaining study IRB and DoD approval. He has worked with study team to draft and finalize case report forms and helped with the development of the study collection tool and OnCore Database. He has coordinated and managed other sites to maintain participation and to begin the onboarding process.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Please see attachment "Collaborating Sites."

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: