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TITLE: Statin Therapy in Patients with Early-Stage ADPKD

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Autosomal dominant polycystic kidney (ADPKD) is the most common monogenic renal disorder accounting 8-10% of patients receiving renal replacement therapy for renal failure worldwide. At present tolvaptan (Jynarque) is the only FDA approved therapy to slow progression of renal disease in the U.S. However, high cost and side effects limit drug prescription. This underlines the need for alternative well-tolerated low cost therapies for ADPKD. Our group has previously shown that pravastatin therapy in children and young adults with ADPKD slowed the increase in total kidney volume due to cyst expansion. The primary goal of the current proposal is to test the efficacy of pravastatin therapy in decreasing renal cyst growth and improving renal function in adults with ADPKD. A secondary goal is to obtain initial insight into the mechanisms by which statins may improve kidney function and structure.

15. SUBJECT TERMS

None Listed

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1. INTRODUCTION

Autosomal dominant polycystic kidney (ADPKD) is the most common monogenic renal disorder accounting 8-10% of patients receiving renal replacement therapy for renal failure worldwide. At present tolvaptan (Jynarque) is the only FDA approved therapy to slow progression of renal disease in the U.S. However, high cost and side effects limit drug prescription. This underlines the need for alternative well-tolerated low cost therapies for ADPKD. Our group has previously shown that pravastatin therapy in children and young adults with ADPKD slowed the increase in total kidney volume due to cyst expansion. The primary goal of the current proposal is to test the efficacy of pravastatin therapy in decreasing renal cyst growth and improving renal function in adults with ADPKD. A secondary goal is to obtain initial insight into the mechanisms by which statins may improve kidney function and structure.

2. KEYWORDS

Autosomal dominant polycystic kidney disease

ADPKD

Kidney Cysts

Cyst growth

Kidney Function

Total kidney volume

Statin therapy

Pravastatin

Glomerular filtration rate

Magnetic resonance imaging

Clinical trial

3. ACCOMPLISHMENTS

The overall goal of this project determine the efficacy of pravastatin in slowing progression of kidney disease in adult patients with ADPKD.

What are the major goals of the project?

1) Prepare regulatory documents and research protocol for the study.
- Timeline months 1-2: Final HRPO approval for the study was obtained 8/29/2017. All internal review board approvals were obtained and the designated milestone achieved.

2) Training study staff for clinical trial
- Timeline months 1-2: This milestone was achieved within the designated time period.

3) Participant recruitment, therapy, participant evaluation.
- Timeline months 2-3: study begins. The first subject was enrolled 11/08/2017, randomized to treatment and baseline assessments completed, milestone achieved.
- Timeline months 3-18 : Recruitment and randomization ongoing. Milestone ~ 66% complete
- Timeline 27-42 months: Complete follow-up assessments. To date 15 subjects have completed their end of study assessments.

4) Data analysis
- Timeline months 42-48: Not started.

What was accomplished under these goals?

Recruitment: Subject recruitment is ongoing and to date 99 subjects have been randomized to treatment arm and have completed the baseline assessments. Baseline visits and pre-screening were put on hold in March 2020 due to University restrictions related to the COVID-19 pandemic.

The current status of recruitment as of 07/31/2020 is detailed below in table 1.

Table 1. Recruitment Status

	Signed consent	Active in study Baseline assessments completed	Screen Fail	Baseline visit scheduled
N	103	84	2	1 on hold

To date 245 additional subjects have been contacted regarding study participation (but have not signed the study consent form) among these 213 do not qualify (please see table 2 for reasons) Note this does not include potential participants identified based on electronic health records (please see next section).

Table 2. Reason for not qualifying for study

	Do not meet inclusion criteria	Already using a statin	Health reason	Pregnancy	Personal reason including interest in tolvaptan
N	86	30	21	12	64

We have obtained internal review board permission to utilize the newly developed COMPASS electronic database (that includes information from the statewide University of Colorado Hospital health facilities) to identify potential subjects for recruitment. To date 88 subjects with ADPKD who are not currently using a statin or tolvaptan have been identified. In conjunction with a nephrologist at the Fort Collins and Colorado Springs facilities we will contact these potential subjects to assess interest in study participation and as appropriate proceed with screening.

Study Intervention: The DSMB board has met 5 times to date and no issues related to the study have been reported.

The intervention has been well-tolerated and no serious adverse events reported. 2 subjects had a minor non-clinically significant elevation in creatine phosphokinase (CPK) and one of these also had a mild elevation in alanine aminotransferase (ALT) level. Two subjects reported muscle pain and fatigue and elected to discontinue drug/placebo but neither had elevated liver function test or CPK levels. Overall, 5 subjects including 2 subjects reporting muscle pain and fatigue have discontinued drug/placebo but remain in the study as intent to treat.

Baseline Analyses: As described in the previous annual report we demonstrated that both Max Q (ml/s) (peak renal blood flow (RBF))($r = 0.52$, $p = 0.05$) and Min Q (ml/s) (minimum RBF)($r = 0.52$, $p = 0.04$) were significantly positively correlated with measured absolute glomerular filtration rate (GFR) ml/min. This relationship was independent of age, sex, systolic blood pressure and body mass index. These data suggest that early hemodynamic alterations may be useful biomarkers of kidney function in early disease. This data was presented as a poster at the annual American Society of Nephrology meeting in Washington DC in November 2019. Published abstract included please see appendix ii.

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

Nothing to Report

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?

In order to increase local (within the state of Colorado) recruitment for the study we have obtained approval from the Colorado Multiple Institutes Review Board to utilize the COMPASS electronic database to identify potential participants for recruitment from the University of Colorado Hospital health facilities in Fort Collins and Colorado Springs. While we are actively working with several out of state potential participants who meet the inclusion criteria, subjects are reluctant to travel to the University during the current COVID-19 pandemic. Thus, we will focus our attention on local recruitment.

4. IMPACT

What was the impact on the development of the principal disciplines(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

Changes in approach and reasons for change

Nothing to Report

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

The COVID-19 outbreak has significantly affected our recruitment of the last 50 subjects needed for the study. In March 2020 our University initiated stringent restrictions for clinical studies, and all travel was shut down. This necessitated extending treatment in a few participants. However, with lifting of the travel restrictions we have been able to bring all of our participants whose end of study visits were put on hold back for their final visit. Baseline visits for out of state participants are delayed, most subjects being reluctant to travel. We are trying to compensate by actively focusing on recruitment of in state participants.

Changes that had a significant impact on expenditure

Slower than expected recruitment during the first year has reduced expenditure for patient related expenses. While recruitment increased over year 2 and first part of year 3, recruitment over the past 5 months has been put on hold due to COVID-19 restrictions. We are actively recruiting again however, overall expenditure is lower due to decreased patient related expenses.

Significant changes in use or care of human subjects.

There have been no significant changes in the use or care of human subjects. Several minor amendments to the approved protocols over the past year have been submitted to the local internal review board for approval and include:

Change to allow use of COMPASS electronic database to allow identification of potential subjects for recruitment.

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:** Michal Schäfer, Petter Bjornstad, Nina Bispham, Zhiying You, Kristen L.Nowak, Katharina Hopp, Godela M.Brosnahan, Michel Chonchol, Berenice Y. Gitomer. Peak renal blood flow

correlates with renal function in adults with ADPKD. J Am Soc Nephrol. 30:341 2109.

- **Website(s) or other internet sites**: Nothing to Report
- **Technologies or techniques:** Nothing to Report
- **Invention's, 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?

Name	Michel Chonchol MD
Project Role	PI
Researcher Identifier	
Nearest person month worked	2
Contribution to Project	Oversight of all clinical aspects of the study
Funding Support	N/A
Name	Berenice Gitomer Ph.D
Project Role	Co-Investigator
Researcher Identifier	
Nearest person month worked	2
Contribution to Project	Patient identification for recruitment, oversight of sample processing for cell isolation
Funding Support	N/A
Name	Nayana Patel MD
Project Role	Co-Investigator (Radiologist)
Researcher Identifier	
Nearest person month worked	1
Contribution to Project	Oversight of all imaging studies including renal blood flow assessment
Funding Support	N/A
Name	Jelena Klawitter Ph.D
Project Role	Co-Investigator
Researcher Identifier	
Nearest person month worked	1
Contribution to Project	Coordination of sample collection and processing for all assays
Funding Support	N/A
Name	Wei Wang MD
Project Role	Co-Investigator
Researcher Identifier	
Nearest person month worked	2
Contribution to Project	Calculation of total kidney volume of all screening and baseline imaging studies
Funding Support	N/N

Name	Beverly Farmer RN
Project Role	Study Coordinator
Researcher Identifier	
Nearest person month worked	12
Contribution to Project	Scheduling patient visits and procedures. Preparation of all regulatory documents for the study
Funding Support	N/A
Name	Zhiying You Ph.D
Project Role	Statistician
Researcher Identifier	
Nearest person month worked	1
Contribution to Project	Subject randomization and study design
Funding Support	N/A

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

New active grants awarded during this funding period are indicated below;

Michel Chonchol MD PI

Active Grants

NIH/NIDDK R01DK121516 (Chonchol) 04/01/2019-03/31/2024

Nicotinamide riboside supplementation for treating arterial stiffness and elevated systolic blood pressure in patients with moderate to severe CKD.

NIH/NIDDK R01DK119649 (Klawitter/Gitomer) 9/01/2018-8/31/2021

The role of inflammation in the progression of polycystic kidney disease

Berenice Gitomer Ph.D Co-Investigator

Active Grants

NIH/NIDDK R01DK121516 (Chonchol) 04/01/2019-03/31/2024
NIH/NIDDK
Nicotinamide riboside supplementation for treating arterial stiffness and elevated systolic blood pressure in patients with moderate to severe CKD.

NIH/NIDDK R01DK119649 (Klawitter/Gitomer) 9/01/2018-8/31/2021

The role of inflammation in the progression of polycystic kidney disease.

Jelena Klawitter Ph.D Co-Investigator

Active Grants

NIH/NIDDK R01DK119649 (Klawitter/Gitomer) 9/01/2018-8/31/2021

The role of inflammation in the progression of polycystic kidney disease

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

Collaborative Awards: N/A

9. APPENDICES
Quad Chart i
ASN Abstract ii