AWARD NUMBER: W81XWH-17-1-0382

TITLE: Statin Therapy in Patients with Early-Stage ADPKD

PRINCIPAL INVESTIGATOR: Michel Chonchol M.D.

CONTRACTING ORGANIZATION: Regents of the University of Colorado
Aurora, CO 80045-2571

REPORT DATE: AUGUST 2019

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
AUGUST 2019	Annual	1AUG2018 - 31JUL2019

4. TITLE AND SUBTITLE
Statin Therapy in Patients with Early-Stage ADPKD

5a. CONTRACT NUMBER
W81XWH-17-1-0382

5b. GRANT NUMBER
PR161645

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Michel Chonchol MD.

E-Mail: Michel.Chonchol@UCDenver.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Regents of the University of
Colorado
13001 East 17th Place
Aurora, CO 80045-2571

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT: The primary goal of this application is to determine the efficacy of pravastatin therapy in slowing progression of kidney disease in patients with autosomal dominant polycystic kidney disease (ADPKD). Subject recruitment is ongoing and to date 73 subjects have been randomized to treatment arm and have completed the baseline assessments. Baseline visits for 5 additional subjects have been scheduled and 3 additional subjects have been pre-screened and their visits are currently being scheduled for an overall total of N = 81 subjects. Recruitment continues and the first subject's 2-year end of study visit will occur in mid-December 2019. There have been no additional screen failures beyond 2 reported in the previous annual report. There has been no drug related serious adverse events and the study is continuing. In a cross-sectional analysis of baseline data from 45 subjects, both peak and minimum renal blood flow rates significantly correlated with measured GFR. This suggests that early alteration in hemodynamic measures may be useful biomarkers of kidney function in early stage ADPKD. An abstract describing this data has been submitted to the 2019 American Society of Nephrology annual meeting scheduled for November.

15. SUBJECT TERMS
Pravastatin clinical trial, Autosomal dominant polycystic kidney disease, kidney disease progression, Randomization, Renal blood flow, Subject recruitment, Inclusion.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	14	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

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 ~ 53% complete
- Timeline 27-42 months: Complete follow-up assessments. Not started

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

What was accomplished under these goals?

Recruitment: Subject recruitment is ongoing and to date 73 subjects have been randomized to treatment arm and have completed the baseline assessments. Baseline visits for 5 additional subjects have been scheduled and 3 additional subjects have been pre-screened and their visits are currently being scheduled for an overall total of N = 81 subjects.

The current status of recruitment as of 07/31/2019 is detailed below in table 1.

Table 1. Recruitment Status

	Signed consent	Active in study Baseline assessments completed	Screen Fail	Baseline visit scheduled
N	75	73	2	5

To date 222 additional subjects have been contacted regarding study participation (but have not signed the study consent form) among these 185 do not qualify (please see table 2 for reasons) and 37 subjects are candidates for recruitment and will continue screening. The study coordinator is actively working with these individuals.

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	76	27	15	10	57

Study Intervention: The DSMB board has met 3 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: Overall, there is good agreement between the measured GFR (mGFR) (Mean ± standard deviation (SD); 89 ± 19) determined by isotope clearance and estimated GFR (eGFR) (92 ± 16) as shown in Figure 1. Although among those with higher GFR there is slightly more divergence in measurements obtained by respective methods as depicted in the Bland Altman plot (Fig.2). The dashed lines show the 95% limits of agreement (from -35.58 to 29.73).

Fig.1

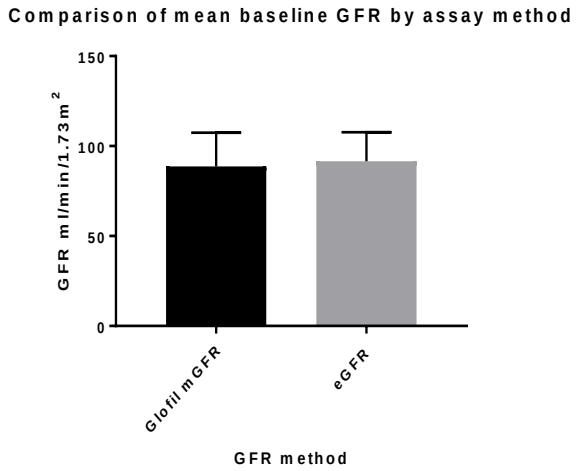
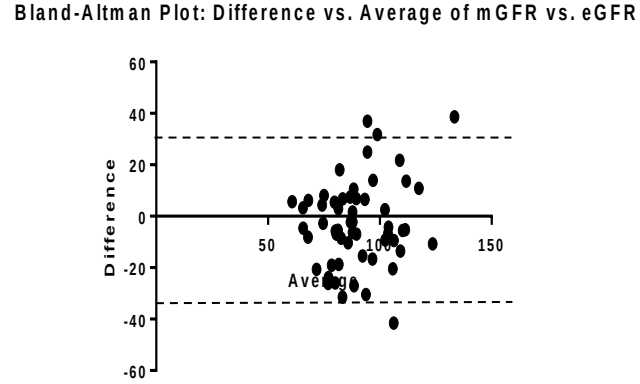


Fig.2



In order to determine whether there is a relationship between parameters of renal flow hemodynamics, we performed an analysis of baseline data from the first forty-five participants (18 male and 27 female) enrolled in the study. Hemodynamic measures were obtained by magnetic resonance imaging (MRI) on a 3.0 T system. (Siemens, Malvern, PA). The participant characteristics are shown in Table 3. 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 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.

Table 3. Demographic characteristics of the study population		
	Mean	**Standard deviation**
Sex M/F	18/27	
Age (years)	41	9
BMI	27.0	6.3
GFR (ml/min)	100.6	28.2
eGFR ml/min/1.73^2	92.3	17.0
Mean Arterial Pressure (mmHg)	94.5	8.5

This data has been submitted as an abstract for the 2019 annual meeting of the American Society of Nephrology scheduled for November.

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 recruitment for the study we have added the Denver Veterans Affairs Hospital as a recruitment site. Local Hospital Review Board approval has been obtained and HRPO approval is currently pending.

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

Overall recruitment has been impacted by FDA approval of tolvaptan (Jynarque) for treatment of patients with polycystic kidney disease. However, the slow recruitment in the first year of the study has been improved over the second year by advertising via email blast through the PKD Foundation and by providing study information to local nephrologists requesting referral of patients interested in the study. We used Facebook to reach additional potential subjects who may not have an active involvement with the PKD Foundation. We will expand direct contact with nephrologists nationally to aid recruitment and have added the Denver VA Hospital as a recruitment site pending HRPO approval.

Changes that had a significant impact on expenditure

Slower than expected recruitment during the first year has reduced expenditure for patient related expenses. However, increased recruitment in year 2 is expected to continue over the coming year with concomitant increase in study 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 inclusion criteria to reduce lower limit of eGFR from 60 ml/min/1.73m^2 to 45 ml/min/1.73m^2 approval date 4/04/2019.

Addition of Denver VA hospital as a recruitment site IRB approval date 4/01/2019 pending HRPO approval.

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:** An abstract title "Peak renal blood flow correlates with renal function in adults with ADPKD" has been submitted for the 2019 upcoming American Society of Nephrology meeting scheduled for November 2019.
- **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) 04/01/2019-03/31/2014

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) 04/01/2019-03/31/2014
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

Statin Therapy in Patients with Early-Stage ADPKD

Insert ERMS/Log Number and Task Title Here: PR161645 Year 2 annual report
Insert Award Number Here: W81XWH-17-1-0382

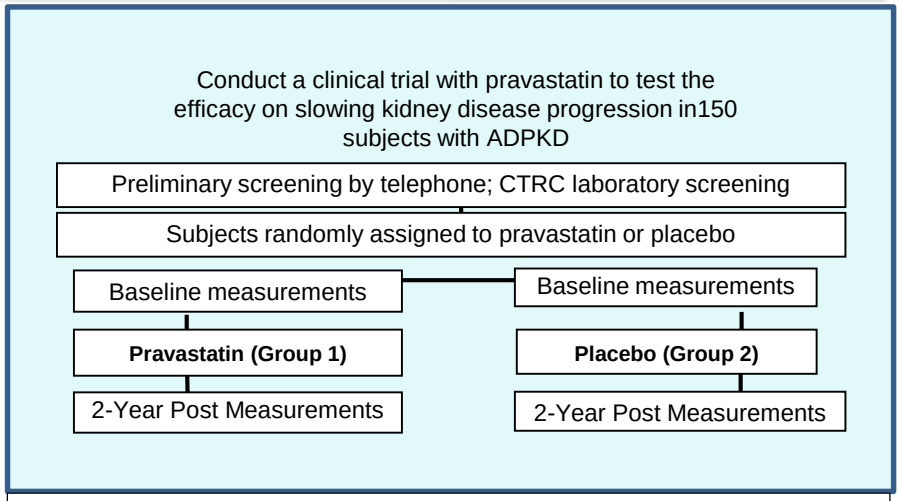
PI: Michel Chonchol M.D. **Org:** Regents of the University of Colorado **Award Amount:** $2,715,191

Study/Product Aim(s)

- Aim 1: To determine total kidney volume measured by MRI before and after 2 years of pravastatin therapy in ADPKD patients
- Aim 2: To determine renal blood flow by magnetic resonance angiography (MRA) and measured glomerular filtration rate (GFR) before and after 2 years of pravastatin therapy in ADPKD patients.
- Aim 3: To measure circulating markers of oxidative stress and inflammation before and after 2 years of pravastatin therapy in ADPKD patients.
- Aim 4: To assess expression of cell cycle regulators and apoptosis related proteins in exfoliated tubular epithelial cells before and after 2 years of pravastatin treatment in ADPKD patients.

Approach

To conduct a double blind placebo controlled trial to test the effectiveness of pravastatin on slowing kidney disease progression in 150 patients with ADPKD.



Accomplishment: Preparation of regulatory documents and staff training completed, prescreening ongoing . Sixty one subjects enrolled, seven additional scheduled.

Timeline and Cost

Activities CY	17	18	19	20
Regulatory documents/training				
Subject screening/recruitment				
Treatment and evaluations				
Data analysis				
Estimated Budget ($K)	$686,024	$684,591	$694,969	$649,607

Updated: (08/01/2019)

Goals/Milestones

CY17 Goal – Prescreening and enrollment
☑ Enroll/consent first participant by month 2
CY18 Goals – Ongoing recruitment and baseline assessments
☐Complete recruitment by month 18
☐Complete 6 week assessments on all subjects
CY19 Goal – Start 2 year assessments
☐ Start 2 year assessments for patients enrolled in year 1
CY20 Goal – Complete study
☐ Complete study assessments and data analysis

Comments/Challenges/Issues/Concerns

- Recruitment is expected to require 1 more year to complete.
- Recruitment impacted by tolvaptan approval as an alternative to entering current research study.

Budget Expenditure to Date

Projected Expenditure: $1,370,615
Actual Expenditure: $979,261

Appendix ii
View Submission

Print

CONTROL ID: 3235067
SUBMISSION TYPE: Research Abstract
TITLE: Peak renal blood flow rate correlates with renal function in adults with ADPKD
AUTHORS: Michal Schäfer[1], Petter Bjornstad[2], Nina Bispham[3], Zhiying You[4], Kristen L. Nowak[5], Katharina Hopp[6], Godela M. Brosnahan[7], Michel Chonchol[3], Berenice Y. Gitomer[1]
INSTITUTIONS: 1. Div. Renal Diseases and Hypertension,, Aurora, CO, United States.
2. University of Colorado School of Medicine, Aurora, CO, United States.
3. University of Colorado , Aurora, CO, United States.
4. UC Denver, Aurora, CO, United States.
5. University of Colorado Denver: Anschutz Medical Campus, Aurora, CO, United States.
6. University of Colorado Denver, AMC, Aurora, CO, United States.
7. University of Colorado Denver, Aurora, CO, United States.
GROUP/TEAM:
ABSTRACT BODY:
Background: Changes in renal blood flow (RBF) occur early in the course of autosomal dominant polycystic kidney disease (ADPKD) and precede the decline in glomerular filtration rate (GFR). The specific hemodynamic factors responsible for the decline in RBF and GFR in ADPKD are poorly defined. The objective of this study was to determine the relationships between flow hemodynamic parameters and GFR in adults with ADPKD.

Methods: All participants provided informed consent and studies were performed in accordance with the Helsinki guidelines. Renal flow indices were obtained by phase-contrast MRI situated in the mid-section of renal arteries. Images were acquired as previously described by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP). GFR was measured by 125I-iothalamate clearance.

Results: Forty-five participants (18 male and 27 female) with a confirmed diagnosis of ADPKD were included in the study. The participant characteristics are shown in Table 1. Both Max Q (ml/s) (peak renal 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 GFR ml/min. This relationship was independent of age, sex, systolic blood pressure and body mass index. However, neither total blood flow volume (ml) or maximum flow velocity (cm/s) correlated with measured GFR.

Conclusion: In this cohort of people with ADPKD with preserved kidney function both peak and minimum RBF rates significantly correlated with measured GFR. These data suggest that early hemodynamic alterations may be useful biomarkers of kidney function in early disease.

TABLE TITLE:
Demographic characteristics of the study population

TABLE:
Demographic characteristics of the study population

Parameter	Mean (N = 45)	Standard deviation
Sex M/F	18/27	
Age (years)	41	9
Body Mass Index	27.0	6.3
Iothalamate GFR (ml/min)	101	28
Estimated GFR (ml/min/1.73m^2)	92	17
Systolic Blood Pressure (mmHg)	124	11

TABLE FOOTER:

(No Image Selected)
FUNDING: Other U.S. Government Support (e.g., Dept. of Defense)
COMMERCIAL SUPPORT:
OTHER NIH SUPPORT:
SUBCATEGORY: 1001 Genetic Diseases of the Kidneys: Cystic
CATEGORY: Genetic Diseases of the Kidneys
DATE/TIME SUBMITTED: May 29, 2019, 12:16 PM