EFFICACY AND SAFETY OF SIROLIMUS IN REDUCING CYST VOLUME IN PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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ABSTRACT

BACKGROUND

Autosomal-Dominant Polycystic Kidney Disease is by far the most frequent inherited kidney disease. In White populations, its prevalence ranges from one in 400 to one in 1000 (Gabow 1993). Though the corresponding figure in Blacks is not yet available, the incidence of ESRD due to ADPKD is similar in American Blacks and Whites (Yium et al, 1994). Renoprotective interventions in ADPKD are maximal reduction of blood pressure and proteinuria and limit the effects of additional potential promoters of disease progression such as dyslipidaemia, chronic hyperglycaemia or smoking. At present, there is no definitive treatment for reducing cyst volume and hence disease progression. Sirolimus (Rapamycin) is an immunosuppressant mostly used for the management of kidney transplant recipients. This drug by specifically and effectively inhibiting mTOR, exerts antiproliferative and growth inhibiting effects and could be important for the inhibition of cyst progression in ADPKD.

MATERIALS AND METHODS

It is an interventional randomised open label, active control study for six months. ADPKD type 1 patients between the age of 18 to 60 years with a GFR > 40 mL/min/1.73 m^2 were included in the study.

RESULTS

Total number of subjects enrolled – 60. Patients enrolled in sirolimus arm – 40. Patients enrolled in conventional treatment arm - 20. Patients dropped out due to sirolimus side effects - 5. Patients lost to followup - 1. Patients completed treatment in conventional treatment arm - 20.

CONCLUSION

Treatment with mTOR inhibitor sirolimus for 6 months was effective in reducing total kidney volume, total renal cyst volume and volume of the largest cyst in patients with ADPKD. There was a small, but significant increase in renal parenchymal volume on treatment with sirolimus. Extending the duration of treatment to one year caused further significant reduction in total kidney volume and cyst volume. Major side effect of sirolimus in our patients was mucositis, which could be managed with topical measures. Sirolimus caused clinically significant anaemia and dyslipidaemia in treated patients.

KEYWORDS

Autosomal Dominant Polycystic Kidney Disease, PKD, Sirolimus.

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BACKGROUND

Autosomal-Dominant Polycystic Kidney Disease is by far the most frequent inherited kidney disease. In White populations, its prevalence ranges from one in 400 to one in 1000 (Gabow 1993).[1] Though the corresponding figure in Blacks is not yet available, the incidence of ESRD due to ADPKD is similar in American Blacks and Whites (Yium et al, 1994).[2] There is a significant level of de novo mutations with a reported rate of 3.6 percent in a series of pedigrees with a PKD1 mutation (Rosetti et al, 2001).[3] At large, ADPKD currently accounts for 3 - 10 percent of all patients admitted for maintenance dialysis in the Western countries. The annual incidence rate of patients with ADPKD treated for ESRD in the United States has not changed over the last decade (United States Renal Data System, 2001).

Renoprotective interventions in ADPKD are maximal reduction of blood pressure and proteinuria and limit the effects of additional potential promoters of disease progression such as dyslipidaemia, chronic hyperglycaemia or smoking. At present, there is no definitive treatment for reducing cyst volume and hence disease progression.

In ADPKD three different genes are implicated which are PKD1 in 78% of the cases, PKD2 in 13% and a probable PKD3 (yet to be identified). PKD1 gene encodes a protein named polycystin-1 (PC1). The PKD1 gene encodes for polycystin-1, a large protein of 4302 amino acids (for review,

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G Wu 2001[4]; Harris 2002[5]; Igarashi and Somlo 2002[6]). Defect in PC1 lead to aberrant activation of the enzyme mTOR in the epithelial cells of the renal tubules, which leads to abnormal proliferation of these cells and cysts generation.

Sirolimus (Rapamycin) is an immunosuppressant mostly used for the management of kidney transplant recipients. This drug by specifically and effectively inhibiting mTOR exerts antiproliferative and growth inhibiting effects and could be important for the inhibition of cyst progression in ADPKD. Animal models of ADPKD have shown that short-term treatment with sirolimus resulted in dramatic reduction of kidney size, prevented the loss of kidney function and lowered cyst volume density. Similarly, retrospective observations from kidney transplant recipients have documented that sirolimus treatment reduced kidney volumes by 25%, whereas there was no effect in patients not given the drug.

Overall, these findings provide the basis for designing a prospective study in ADPKD patients aimed to document the efficacy of sirolimus treatment in preventing further increase or even reducing the total kidney volume and the renal volume taken up by cysts, halting kidney disease progression. It is a 6-month study with sirolimus compared to conventional therapy in adult patients with ADPKD and normal renal function or mild-to-moderate renal insufficiency.

OBJECTIVE

To assess the efficacy and safety of 6-month treatment with sirolimus (along with conventional therapy) as compared to conventional therapy alone in adult patients with ADPKD and normal renal function or mild-to-moderate renal insufficiency.

MATERIALS AND METHODS

Study Type - Interventional.
Study Design - Randomised open label, active control.
Duration - 6 months.
Randomisation - Randomised at a two-to-one ratio to sirolimus or standard treatment alone.

Inclusion Criteria

- ADPKD type 1 patients after genetic typing
- Age 18 years - 60 years
- GFR > 40 mL/min/1.73 m2
- Urinary protein excretion rate < 0.5 g/24 hrs.
- Written informed consent

Exclusion Criteria

- Urinary protein excretion rate > 0.5 g/24 hrs. or abnormal urinalysis suggestive of concomitant, clinically significant glomerular disease
- Diabetes mellitus
- Active malignancy
- Psychiatric disorders or any condition that might prevent full comprehension of the purposes and risks of the study
- Infection with hepatitis B or C, HIV
- Pregnancy, lactation or child bearing potential and ineffective contraception
- Increased liver enzymes (2-fold above normal values)
- Hypercholesterolaemia (fasting cholesterol > 8 mmol/L) or hypertriglyceridaemia (> 5 mmol/L) not controlled by lipid lowering therapy
- Granulocytopaenia (white blood cell < 3,000/mm3) or thrombocytopaenia (platelets < 100,000/mm3)
- Co-medication with strong inhibitor of CYP3A4 and/or P-gp like voriconazole, ketoconazole, diltiazem, verapamil, erythromycin or with a strong CYP3A4 and or P-gp inductor-like rifampicin
- Known hypersensitivity to macrolides or sirolimus
- Randomised, longitudinal study with a baseline evaluation and 6-month treatment period with sirolimus given in addition to conventional anti-hypertensive therapy.

- **Conventional Therapy limb** - All patients were put on renoprotective measures - angiotensin converting enzyme inhibitors/angiotensin receptor blockers, statins and calcitriol. Other antihypertensives were continued or added depending on the blood pressure levels to attain target BP (< 135/85 mmHg). This approach aimed to minimise the confounding effect of any change in concomitant treatments on some efficacy variables (such as urinary protein excretion rate).

- **Sirolimus limb** - Patients were started on sirolimus at the oral daily dose of 2 mg along with the conventional treatment. The daily dose was adjusted to keep the whole blood trough level of sirolimus concentration within 5 - 10 ng/mL. Drug levels were assessed at day 14 and at the end of 3 months after starting treatment.

MAGNETIC RESONANCE IMAGING - RENAL VOLUME MEASUREMENTS

- All patients underwent MR imaging of the kidneys. The imaging protocol included unenhanced sequences 3D FIESTA. A manual segmentation of both kidneys is performed for each patient. To prevent bias, the observer was blinded to all clinical and radiological data, first measurements. Each kidney was assessed separately. The vessels and the ureter in the area of the renal hilum were excluded from manual volumetric marking. The volume corresponding to each outline was obtained by multiplying the area of the outline by the section thickness. The total volume of the kidney segments is obtained by summing the volume of each section.
- Total cyst volume was assessed and renal parenchymal volume calculated by subtracting cyst volume from parenchymal volume.
- Volume of the largest cyst was assessed pre and post treatment.

FOLLOWUP

Two main study visits included MRI and 24 hrs. urine collection at baseline and 6 months. Three additional visits including clinical assessment and blood and urine chemistry at months 1, 3 and 6. Patients in the treatment arm will have four extra visits at week 2, 4, month 1 and 2 after randomisation.

RESULTS AND DISCUSSION

- Total number of subjects enrolled – 60
- Patients enrolled in sirolimus arm – 40
- Patients enrolled in conventional treatment arm - 20
- Patients dropped out due to sirolimus side effects - 5
- Patients lost to followup - 1.
- Patients completed treatment in sirolimus arm - 34.
- Patients completed treatment in conventional treatment arm - 20.

	Sirolimus Group	**Control Group**
Age (< 40 yrs.)	32.3%	30%
Gender (Males)	44.1 %	35%
History of hypertension	76.5%	65%
Baseline Characteristics		

	Baseline		**6 Months**	
	Sirolimus Group	**Control Group**	**Sirolimus Group**	**Control Group**
Mean Weight (kg)	58.47	56.40	59.25	57.82
BMI	21.356	20.479	21.5	20.98
Mean SBP (mmHg)	133.36	132.30	132.59	132.60
Mean DBP (mmHg)	85.35	81.70	84	82.63
Weight and Blood Pressure Baseline vs. 6 Months				

Mean Values	**Sirolimus Group**	**Control Group**	**P value**
S. creatinine (mg/dL)	1.135	1.070	0.399
Measured GFR Creatinine clearance (mL/min/per 1.73 m²)	79.656	78.444	0.112
U. protein (g/24 hours)	181.24	148.40	0.193
Hb (g/dL)	12.503	11.375	0.012
WBC count (L/mm³)	7455	7760	0.014
Platelet (L/mm³)	3.624	3.300	0.086
S. cholesterol (mg/dL)	202.82	213.05	0.224
LDL (mg/dL)	118.15	109.40	0.103
TGL (mg/dL)	148.9	130.85	0.160
AST (IU/L)	28.44	30.30	0.427
ALT (IU/L)	33.24	30.800	0.407
Baseline Labs			

The two groups were comparable in their baseline characteristics and lab values.
Sirolimus trough blood levels averaged 6.9 ± 2.8 ng/mL.

Mean Values	**Sirolimus Group**			**Control Group**		
	Baseline	**After 6 Months**	**p value**	**Baseline**	**After 6 Months**	**P value**
S. creatinine (mg/dL)	1.135	1.016	0.403	1.070	1.134	0.061
Measured GFR Creatinine clearance (mL/min/per 1.73 m²)	79.656	80.4	0.438	78.444	77.4	0.211
U. protein (g/24 hours)	181.24	229.47	0.000	148.40	153.80	0.174
Hb (g/dL)	12.503	11.51	0.000	11.375	11.46	0.486
WBC count (L/mm³)	7455	7300	0.000	7760	7760	1.000
Platelet (L/mm³)	3.624	3.394	0.001	3.300	3.270	0.522
S. cholesterol (mg/dL)	202.82	228.76	0.000	213.05	215.75	0.422
LDL (mg/dL)	118.15	132.53	0.000	109.40	111.55	0.292
TGL (mg/dL)	148.9	177.06	0.000	130.85	128.65	0.520
AST (IU/L)	28.44	31.652	0.000	30.30	30.00	0.795
ALT (IU/L)	33.24	36.510	0.000	30.800	30.870	0.941
Change in Lab Values in Each Group at 6 Months						

There was statistically and clinically significant increase in proteinuria, total cholesterol, LDL and triglycerides and decrease in haemoglobin values in sirolimus arm vs conventional arm at the end of 6 months.

There was clinically insignificant fall in total WBC count, platelet count and increase in liver enzymes in sirolimus arm vs conventional arm at the end of 6 months.

	Sirolimus Group				Control Group			
MRI Findings	**Baseline (mean±SD)**	**After 6 Months (mean±SD)**	**Diff: in mean vol. (Baseline – 6 months)**	**P**	**Baseline (mean±SD)**	**After 6 months (mean±SD)**	**Diff: In mean vol. (Baseline - 6 months)**	**P**
Total kidney volume (mL)	1230.38 ±534.309	12O7.706 ±535.72	22.675 ±58.8	.031	1029.757± 635.19	1049.63± 639.908	-19.8747 ±15.64	0.00
Cyst volume (mL)	948.989 ±536.90	922.86 ±537.74	26.125 ±59.69	0.02	775.313± 638.831	796.02± 643.169	-20.707 ±16.7	0.00
Parenchymal volume (mL)	281.30 ±30.83	284.838 ±31.46	-3.5330 ±3.92	0.00	257.4435± 19.20	256.215± 19.896	1.2282 ±4.7	0.26
Largest cyst volume (mL)	94.994 ±60.485	87.411 ±55.414	7.583 ±14.4	0.004	67.96± 33.59	72.888± 35.72	-4.926 ±3.66	0.00
MRI Findings (Baseline vs. 6 Months)								

Statistically significant reduction in total kidney volume, total cyst volume, largest cyst volume and increase in renal parenchymal volume in sirolimus arm vs conventional arm at the end of 6 months.

Mean Volumes	**Baseline**	**6 Months**	**1 Year**	**Diff: In Baseline and 6 Months**	**Diff: In 6 Months and 1 Year**
Total Kidney Volume (mL)	1310.26	1246.25	1153.602	63.87	96.6488**
Cyst Volume (mL)	1030.769	960.99	869.366	69.77	93.6324***
Parenchymal Volume (mL)	279.351	285.22	286.236	-5.90040**	-0.98380
Largest Cyst Volume (mL)	117.336	111.059	100.108	10.951	17.2282
Subgroup Analysis of Patients Who Took Sirolimus for 1 Year (Number of Patients 5)					

P value * < 0.05
** < 0.01
*** < 0.001

Statistically significant reduction in total kidney volume and total cyst volume when sirolimus treatment was extended for 1 year.

Mucositis	26 (76.5%)
Bone marrow suppression necessitating stoppage of drug	2 (5.8%)
Haemoglobin drop (≥ 1 g/dL)	17 (50%)
Infection (respiratory/pyoderma)	6 (17.6%)
Hypercholesterolaemia	30 (88.2%)
Increase in Proteinuria (≥ 30 mg)	19 (55.8%)
Side Effect Profile of Sirolimus	

CONCLUSION

1. Treatment with mTOR inhibitor sirolimus for 6 months was effective in reducing total kidney volume, total renal cyst volume and volume of the largest cyst in patients with ADPKD.
2. There was a small, but significant increase in renal parenchymal volume on treatment with sirolimus.
3. Extending the duration of treatment to one year caused further significant reduction in total kidney volume and cyst volume.
4. Major side effect of sirolimus in our patients was mucositis, which could be managed with topical measures.
5. Sirolimus caused clinically significant anaemia and dyslipidaemia in treated patients.

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