ORIGINAL ARTICLE

Everolimus in Patients with Autosomal Dominant Polycystic Kidney Disease

Gerd Walz, M.D., Klemens Budde, M.D., Marwan Mannaa, M.D., Jens Nürnberger, M.D., Christoph Wanner, M.D., Claudia Sommerer, M.D., Ulrich Kunzendorf, M.D., Bernhard Banas, M.D., Walter H. Hörl, M.D., Ph.D., Nicholas Obermüller, M.D., Wolfgang Arns, M.D., Hermann Pavenstädt, M.D., Jens Gaedeke, M.D., Martin Büchert, Ph.D., Christoph May, Ph.D., Harald Gschaidmeier, Ph.D., Stefan Kramer, Ph.D., and Kai-Uwe Eckardt, M.D.

ABSTRACT

BACKGROUND

Autosomal dominant polycystic kidney disease (ADPKD) is a slowly progressive hereditary disorder that usually leads to end-stage renal disease. Although the underlying gene mutations were identified several years ago, efficacious therapy to curtail cyst growth and prevent renal failure is not available. Experimental and observational studies suggest that the mammalian target of rapamycin (mTOR) pathway plays a critical role in cyst growth.

METHODS

In this 2-year, double-blind trial, we randomly assigned 433 patients with ADPKD to receive either placebo or the mTOR inhibitor everolimus. The primary outcome was the change in total kidney volume, as measured on magnetic resonance imaging, at 12 and 24 months.

RESULTS

Total kidney volume increased between baseline and 1 year by 102 ml in the everolimus group, versus 157 ml in the placebo group (P=0.02) and between baseline and 2 years by 230 ml and 301 ml, respectively (P=0.06). Cyst volume increased by 76 ml in the everolimus group and 98 ml in the placebo group after 1 year (P=0.27) and by 181 ml and 215 ml, respectively, after 2 years (P=0.28). Parenchymal volume increased by 26 ml in the everolimus group and 62 ml in the placebo group after 1 year (P=0.003) and by 56 ml and 93 ml, respectively, after 2 years (P=0.11). The mean decrement in the estimated glomerular filtration rate after 24 months was 8.9 ml per minute per 1.73 m^2 of body-surface area in the everolimus group versus 7.7 ml per minute in the placebo group (P=0.15). Drug-specific adverse events were more common in the everolimus group; the rate of infection was similar in the two groups.

CONCLUSIONS

Within the 2-year study period, as compared with placebo, everolimus slowed the increase in total kidney volume of patients with ADPKD but did not slow the decline in progressive renal impairment. (EudraCT number, 2006-001485-16; ClinicalTrials.gov number, NCT00414440.)

From the University Hospital, Freiburg (G.W., M.B.); Charité Universitätsmedizin Berlin Campus Mitte (K.B., J.G.) and Campus Virchow (M.M.), Berlin; University Hospital of Duisburg-Essen, Essen (J.N.); University Hospital, Würzburg (C.W.); University Hospital, Heidelberg (C.S.); University Hospital, Kiel (U.K.); University Hospital, Regensburg (B.B.); University Hospital, Frankfurt (N.O.); Merheim Medical Center, Cologne (W.A.); University Hospital, Münster (H.P.); Novartis Germany, Nuremberg (C.M., H.G., S.K.); and University of Erlangen and Community Hospital Nürnberg, Erlangen (K.-U.E.) — all in Germany; and Medical University of Vienna, Vienna (W.H.H.). Address reprint requests to Dr. Walz at the Renal Division, University Hospital Freiburg, Hugstetter St., 55 79106 Freiburg, Germany, or at gerd.walz@uniklinik-freiburg.de.

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Autosomal dominant polycystic kidney disease (ADPKD) affects approximately 1 of every 1000 persons in the general population[1] and develops, by means of slowly progressive renal-cyst growth, to end-stage renal disease in over 50% of patients. Hepatic and pancreatic cysts, as well as cerebral and abdominal aneurysms, contribute to ADPKD-associated morbidity and mortality. Arterial hypertension, recurrent urinary tract infection, nephrolithiasis, and abdominal pain are frequently the presenting symptoms.[2]

Approximately 85% of patients with ADPKD have mutations in the polycystic kidney disease 1 gene (*PKD1*), whereas most of the remaining 15% have polycystic kidney disease 2 gene (*PKD2*) mutations and generally milder manifestations.[3] The *PKD1* and *PKD2* gene products — making up the polycystin protein complex — are located in the primary, nonmotile cilium, a microtubular organelle present on most cells in the body.[4] The polycystin protein complex translates mechanochemosensory signals; however, the precise molecular functions of the individual proteins, and thus specific therapies, have remained elusive.

Dysregulation of the mammalian target of rapamycin (mTOR) kinase is hypothesized to promote cyst formation and disease progression. The mTOR inhibitor sirolimus suppresses cyst growth and mitigates the increase in total kidney volume in animal models of cystic kidney disease[5-7]; similar results have been reported for the mTOR inhibitor everolimus.[8] Two retrospective analyses of patients with ADPKD who had received a kidney transplant showed that treatment with mTOR inhibitors reduce volumes of both the kidney and liver, unlike other classes of immunosuppressive drugs.[6,9]

Although several drugs effectively suppress cyst growth in cystic animal models, there is a lack of medical therapy proven to slow the progression of ADPKD. In this study, we examined the use of everolimus in treating ADPKD.

Methods

Study Design

We performed a randomized, double-blinded, placebo-controlled trial to test the efficacy of everolimus in ADPKD; an academic executive committee in collaboration with the medical and statistical staff of Novartis (the sponsor) designed the study. Data collection and management were the responsibility of the sponsor; patient safety was monitored by an independent data and safety monitoring board.

The institutional ethics committee at each site approved the protocol; all patients provided written informed consent. Everolimus (Certican) and placebo were provided by the sponsor. The study was conducted in accordance with Good Clinical Practice standards, including the Declaration of Helsinki (modified in 1996). Enrollment began on December 5, 2006, and ended on September 18, 2007. The unblinded interim analysis and the final analysis were performed by Winicker (Nuremberg, Germany), which provided the authors with unrestricted access to the data.

The manuscript was prepared by the principal (academic) investigator and revised by the authors. All authors agreed to submit the article for publication and assume responsibility for the accuracy and completeness of the data and analyses. The study was conducted in accordance with the protocol, including the statistical-analysis plan (available with the full text of this article at NEJM.org). The protocol-development committee, data and safety monitoring board, and study team are listed in the Appendix. Additional information regarding the investigators and study sites is contained in the Supplementary Appendix (also available at NEJM.org).

Study Population

Patients were recruited from 24 academic centers in three countries. Eligibility criteria were a clinical diagnosis of both ADPKD and stage II or III chronic kidney disease (i.e., an estimated glomerular filtration rate [GFR], calculated using the reexpressed Modification of Diet in Renal Disease formula,[10] of 30 to 89 ml per minute per 1.73 m^2 of body-surface area) or stage I chronic kidney disease (i.e., estimated GFR ≥90 ml per minute) plus an estimated single kidney volume exceeding 1000 ml. Exclusion criteria were subarachnoid bleeding, severe infection, life-threatening urinary tract or cyst infection, severe liver disease, cancer, hypercholesterolemia (i.e., total cholesterol level ≥352 mg per deciliter [9.1 mmol per liter]), hypertriglyceridemia (i.e., triglyceride level ≥496 mg per deciliter [5.6 mmol per liter]), thrombocytopenia (i.e., platelet count ≤100,000 per cubic millimeter), and a medical condition necessitating long-term anticoagulation therapy.

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STUDY PROCEDURE

Eligible patients were randomly assigned, in a 1:1 ratio, to receive either everolimus at a dose of 2.5 mg twice a day or placebo (the equivalent number of tablets). Everolimus levels were centrally monitored, in the Clinical Chemistry Department at University Hospital Göttingen (Göttingen, Germany). The everolimus dose was set at levels that prevent organ rejection and was adjusted to achieve a trough level between 3 and 8 ng per milliliter; corresponding dose adjustments were made for placebo. Discontinuation of the study drug was permitted for 4 consecutive weeks, and a maximum of 8 cumulative weeks, within the 24-month study, a length of time postulated not to affect the primary outcome. Clinical chemical measurements, including creatinine levels, and spot urine samples were obtained at individual study sites at weeks 1, 2, and 4 and at months 3, 6, 9, 12, 18, and 24.

SAFETY MONITORING

The data and safety monitoring board reviewed the safety reports in an ongoing fashion and performed an interim analysis at 12 months, with the authority to terminate the study because of safety concerns or if there was a difference in the study-drug effect between the two groups with a P value below 0.01, as calculated with the use of a Bonferroni-type method with boundaries sufficient to maintain the overall significance of the study at a two-sided alpha level of 0.05.[11] The nominal two-sided adjusted significance levels were 1% for the interim analysis and 4% for the final analysis. The data and safety monitoring board did not recommend altering or terminating the study on the basis of the interim data.

OUTCOME MEASURES

The primary outcome was the change in total kidney volume, as measured on magnetic resonancy imaging (MRI). A protocol developed by the Magnetic Resonance Development and Application Center Freiburg (MRDAC) was used at all sites, according to published techniques (see the Supplementary Appendix for details).[12,13] After the MRI scans were made anonymous by Clinstud (Hetlingen, Germany), they were evaluated by an independent reviewer at MRDAC who was unaware of the study-drug assignment, to determine total kidney and cyst volumes. The baseline kidney MRI was performed during the first week after enrollment, as well as at 12 and 24 months. The maximal interval between the baseline, 12-month, and 24-month visit and the performance of the MRI for that time point was 4 weeks. Patients who discontinued the study drug had a final examination and MRI scheduled.

Secondary outcomes were changes from the baseline value in the mean cyst and parenchymal volumes at months 12 and 24 and in renal function at month 24. Renal function was measured as the estimated GFR, the serum creatinine level, the urinary protein:creatinine ratio, and the incidence of newly developed end-stage renal disease. Other secondary outcomes were the safety and tolerability of everolimus, changes in blood pressure between baseline and 24 months, and overall survival.

STATISTICAL ANALYSIS

The study was designed to detect a 50% relative reduction in the annual increase in total kidney volume in the everolimus group as compared with the placebo group. Assuming that the increase in the mean (±SD) total kidney volume was 64±70 ml per year,[14] clinically meaningful improvement was defined as an increase in total kidney volume of 32 ml per year. We estimated that 130 patients would need to be enrolled in each study group to provide 90% statistical power to detect the 50% relative reduction, with a two-sided significance level of 4%.

The sample size was set at 400 patients to allow for dropout, a larger-than-estimated standard deviation, or a smaller-than-expected study-drug effect. The intention-to-treat analysis included data for all patients randomly assigned to receive everolimus or placebo who underwent MRI at least once after the baseline visit. The data in the two groups were compared with the use of analysis of covariance. Missing values for the total kidney volume were imputed by means of a multiple-imputation procedure.[15]

Changes in the estimated GFR were summarized on the basis of observed values, according to visit and study group. The annual rate of change in the estimated GFR was calculated as the slope of a linear regression model. The statistical-analysis plan, including the definition of subgroups for efficacy analyses, was finalized before the trial data were unblinded and analyzed. Major protocol violations, defined in the study protocol, were identified and assessed in a

blinded data-review meeting before the database was locked, the study-drug assignment unblinded, and the data analyzed.

RESULTS

PATIENTS

A total of 392 patients were enrolled at 16 academic centers in Germany, 25 patients at 3 academic centers in Austria, and 35 patients at 5 academic centers in France. Of these 452 patients, 433 were randomly assigned to receive everolimus or placebo; 2 of the 433 withdrew consent (Fig. 1). Of the remaining 431 patients, 329 (76.3%) completed the study. The dropout rate was higher in the everolimus group (32.7% of patients) than in the placebo group (14.7%). The two study groups were well balanced with respect to baseline characteristics (Table 1). The mean age was 44 years, and 49% of the patients were women. Nearly all patients were white and had a family history of ADPKD. Patients received a diagnosis of ADPKD an average of 18 years before enrollment. Hypertension was present in 88% of patients. The mean estimated GFR was similar in the two groups. The urinary protein:creatinine ratio (for which protein was measured in milligrams per liter and creatinine in grams per liter) at baseline was 337 in the everolimus group and 398 in the placebo group. The baseline total kidney volume was 2028±1173 ml in the everolimus group and 1911±1153 ml in the placebo group. There was a strong correlation between cyst and total kidney volume ($r^2=0.92$) (Fig. 2A) but a lack of correlation between baseline total kidney volume and estimated GFR (Fig. 2B).

The mean trough level of everolimus in the everolimus group was 5.3 ng per milliliter (interquintile range, 2.9 to 6.6) (Fig. 1 in the Supplementary Appendix). A total of 59% of the measurements were within the target range of 3 to 8 ng per milliliter, with 26% below and 15% above.

CHANGES IN TOTAL KIDNEY VOLUME

Among patients receiving everolimus, the mean total kidney volume increased from 2028 ml to 2063 ml at 1 year and to 2176 ml at 2 years, and among those receiving placebo, it increased from 1911 ml to 2061 ml and to 2287 ml, respectively. The mean changes in total kidney volume, calculated on the basis of observed values, were 101 ml and 239 ml for the everolimus group and 157 ml and 319 ml for the placebo group at years 1 and 2, respectively. The least-square mean differences between the everolimus group and the placebo group, after adjustment for missing values, were 54 ml at 1 year (P=0.02) and 71 ml at 2 years (P=0.06) (Fig. 2C and Table 2).

The cyst volume increased by 76 ml at 1 year and 181 ml at 2 years in the everolimus group and by 98 ml and 215 ml, respectively, in the placebo group (Table 2). The least-squares mean differences between the everolimus group and the placebo group, after adjustment for missing values, were 22 ml at 1 year (P=0.27) and 33 ml at 2 years (P=0.28). The parenchymal volume increased by 26 ml at 1 year and by 56 ml at 2 years in the everolimus group; the corresponding changes in the placebo group were 62 and 93 ml (Table 2). The least-squares mean differences between the everolimus group and the placebo group, after adjustment for missing values, were 36 ml at 1 year (P=0.003) and 37 ml at 2 years (P=0.11).

EFFECTS ON SECONDARY OUTCOMES

Renal Outcomes

The estimated GFR decreased by 8.9 ml per minute in the everolimus group and 7.7 ml per minute in the placebo group (P=0.15) over the 2-year study period (Fig. 2D). The annual decrement in the estimated GFR was 5.5 ml per minute in the everolimus group and 3.5 ml per minute in the placebo group, based on a linear regression model (P<0.001). The estimated GFR increased initially, but then declined more severely from 6 to 18 months, in the everolimus group than in the placebo group (Table 1 in the Supplementary Appendix). Thus, during the first year of the study, although treatment with everolimus significantly slowed the increase in total kidney volume (P=0.02), it was associated with a greater decline in the estimated GFR (by 5.4 ml per minute) than placebo (with a decline of 3.2 ml per minute) (P=0.004) (Table 1 in the Supplementary Appendix). These findings, together with the lack of correlation between changes in total kidney volume and estimated GFR (Fig. 2B), indicate that slowing the progression of kidney enlargement does not necessarily improve renal function.

End-stage renal disease occurred in one patient in the everolimus group. In addition, one patient in each of the two groups received a kidney transplant during the 2-year study period.

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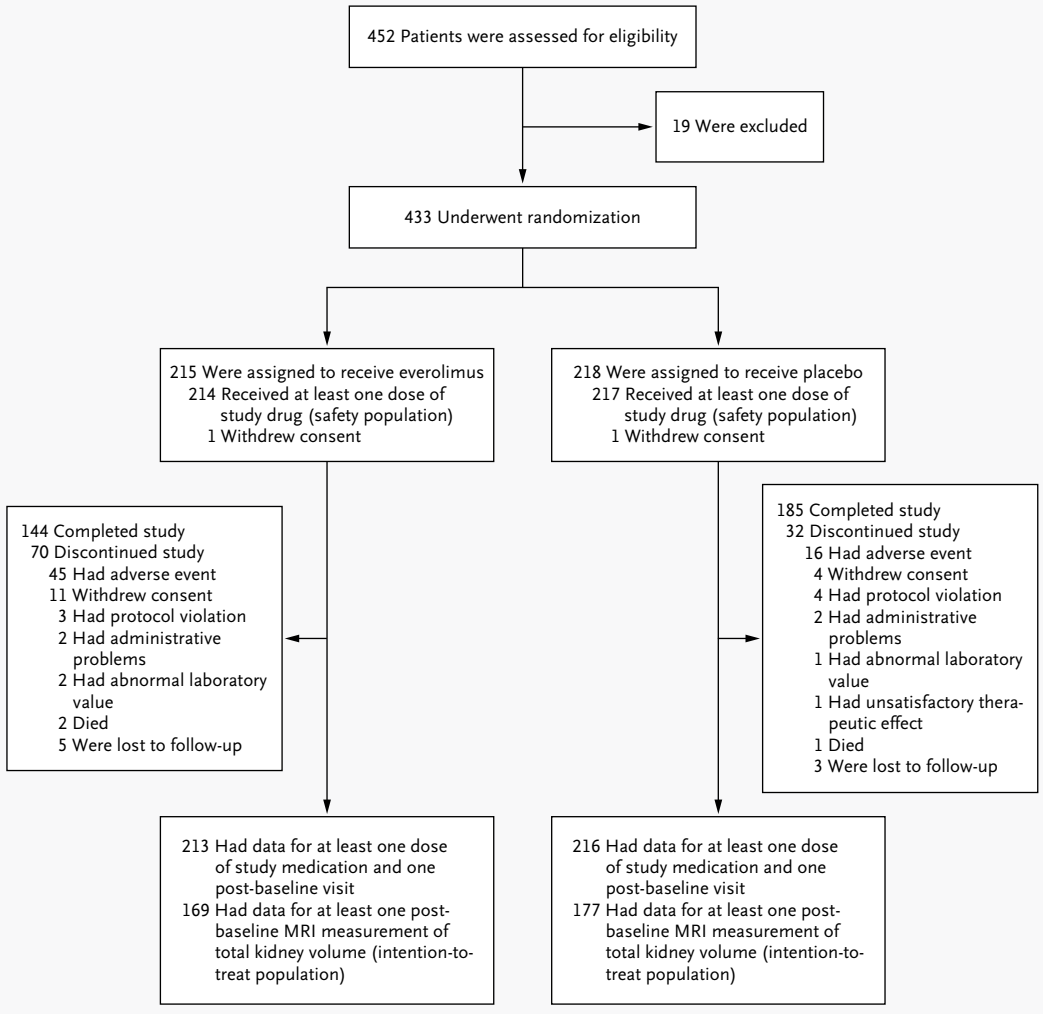

Figure 1. Enrollment, Randomization, and Follow-up of the Study Patients with Autosomal Dominant Polycystic Kidney Disease.

Proteinuria

The mean urinary protein:creatinine ratio at baseline was 337±478 in the everolimus group and 398±1058 in the placebo group. At 2 years, the mean ratio was similar in the placebo group (393±936) but had increased to 564±1177 in the everolimus group (P=0.008) (Fig. 2 in the Supplementary Appendix). Between baseline and 2 years, the percentage of patients with subnephrotic proteinuria (i.e., a urinary protein:creatinine ratio of 300 to <3000) increased from 22.7% to 34.7% in the everolimus group and from 18.2% to 24.3% in the placebo group. By 2 years, nephrotic proteinuria (i.e., a urinary protein:creatinine ratio of ≥3000) had developed in three patients in the everolimus group and one patient in the placebo group.

Lipid Profile

As anticipated, over the 2-year study period, everolimus treatment led to an increase in the total cholesterol level, from 205 to 228 mg per deciliter (5.3 to 5.9 mmol per liter), and in the triglyceride level, from 133 to 204 mg per deciliter (1.5 to 2.3 mmol per liter); lipid profiles were unchanged in the placebo group (Table 3A in the Supplementary Appendix). The use of lipid-lowering agents, in approximately 13% of the study

patients before enrollment, increased to 39.9% in the everolimus group and to 21.3% in the placebo group after enrollment (P<0.001) (Table 3B in the Supplementary Appendix).

Adverse Events and Death

Everolimus treatment was associated with known side effects, including leukopenia, thrombocytopenia, and hyperlipidemia (Table 3). The rates of acne and stomatitis were higher with everolimus than with placebo, and these conditions occurred during the first months of the study. Despite its immunosuppressive action, everolimus was not associated with a significantly increased number of infections. In particular, the number of urinary tract infections was similar in the two groups.

Angioedema occurred in 12 of 214 patients (5.6%) in the everolimus group, all among patients who were also receiving angiotensin-converting–enzyme (ACE) inhibitors. After the data and safety monitoring board issued a directive

Table 1. Baseline Characteristics of the Study Patients, According to Study Group.*

Characteristic	Everolimus N=213	Placebo N=216	P Value†
Population with at least one dose of study drug and one post-baseline visit			
Age — yr	44.5±10.1	44.4±10.5	0.94
Female sex — no. (%)	109 (51.2)	100 (46.3)	0.34
Race — no. (%)‡			
White	207 (97.2)	216 (100.0)	
Black	1 (0.5)	0	
Asian	4 (1.9)	0	
Other	1 (0.5)	0	
Basis of diagnosis — no. (%)			0.25
Family history	211 (99.1)	216 (100.0)	
Other	2 (0.9)	0	
Time since first diagnosis — mo	228.2±118.5	220.2±111.2	0.47
First symptom — no. (%)			0.96
None (accidental discovery)	69 (32.4)	75 (34.7)	
Hematuria	14 (6.6)	14 (6.5)	
Pain	19 (8.9)	19 (8.8)	
Other	111 (52.1)	108 (50.0)	
Body-mass index§	25.7±4.0	26.0±4.4	0.49
Hypertension — no. (%)	187 (87.8)	190 (88.0)	1.00
Blood pressure — mm Hg			
Systolic	136.3±15.5	135.3±17.1	0.53
Diastolic	87.8±10.9	87.5±10.0	0.76
Serum creatinine — mg/dl	1.42±0.46	1.36±0.44	0.21
Estimated GFR — ml/min/1.73 m^2	53.0±19.8	56.0±19.9	0.12
Urinary total protein:creatinine ratio¶	337±478	398±1058	0.51
Blood-pressure medication — no. (%)	187 (87.8)	190 (88.0)	1.00
Agents acting on RAS	170 (79.8)	173 (80.1)	1.00
Beta-blocker	90 (42.3)	86 (39.8)	0.63
Calcium-channel blocker	54 (25.4)	51 (23.6)	0.74
Diuretic	55 (25.8)	41 (19.0)	0.11

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Table 1. (Continued.)

Characteristic	Everolimus N=213	Placebo N=216	P Value†
Patients with at least one post-baseline MRI scan (intention-to-treat population)	**N=169**	**N=177**	
Total kidney volume — ml			
Mean	2028±1173	1911±1153	0.35
Minimum	308	458	
Median	1706	1612	
Maximum	7681	6915	
Cyst volume — ml			
Mean	1202±921	1079±836	0.19
Minimum	56	99	
Median	900	799	
Maximum	6091	5687	
Parenchymal volume — ml			
Mean	826±411	831±433	0.91
Minimum	205	247	
Median	756	744	
Maximum	2380	2792	

* Plus–minus values are means ±SD. To convert values for creatinine to millimoles per liter, multiply by 88.4. GFR denotes glomerular filtration rate, MRI magnetic resonance imaging, and RAS renin–angiotensin system.
† P values were calculated with the use of the t-test, except P values for female sex, diagnosis, first symptom, hypertension, and blood-pressure medication, which were calculated with the use of Fisher's exact test.
‡ Race was self-reported.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ In the urinary total protein:creatinine ratio, protein was measured in milligrams per liter and creatinine in grams per liter.

to shift patients from ACE inhibitors to angiotensin-receptor blockers before receiving everolimus, no further cases of angioedema were reported. Diuretics were used slightly more often in the everolimus group than in the placebo group; the increased use of diuretics was probably the result of peripheral edema, diagnosed in 44 of the 214 patients (20.6%) treated with everolimus and in 20 of 217 patients (9.2%) treated with placebo. The change from baseline in the systolic blood pressure at 24 months was –2.0 mm Hg in the everolimus group and –1.5 mm Hg in the placebo group (P=0.76); the corresponding changes in diastolic blood pressure were –2.7 mm Hg and –2.6 mm Hg (P=0.89).

Two patients (0.9%) in the everolimus group died. One died from pancreatic cancer. The other had severe mitral regurgitation, and progressive heart failure developed during the study; the patient died from cardiogenic shock 18 days after discontinuation of everolimus. One patient (0.5%) in the placebo group died, from pancreatic cancer.

DISCUSSION

The lengthy clinical course of ADPKD makes it difficult to develop effective preventive treatment. Renal function is maintained for many years, despite progressive cyst growth and the loss of normal tissue. Not until total kidney volume reaches 1500 ml does kidney enlargement correlate predictably with the decline in the GFR — at a decrement of 5% per year (or approximately 5 ml per minute per year).[14] We studied patients with large kidneys and renal dysfunction to determine whether everolimus slows the increase in total kidney volume in patients with ADPKD. As compared with placebo, everolimus slowed the increase in total kidney volume during the first year (P=0.02), but the significant effect was not maintained after 2 years, possibly

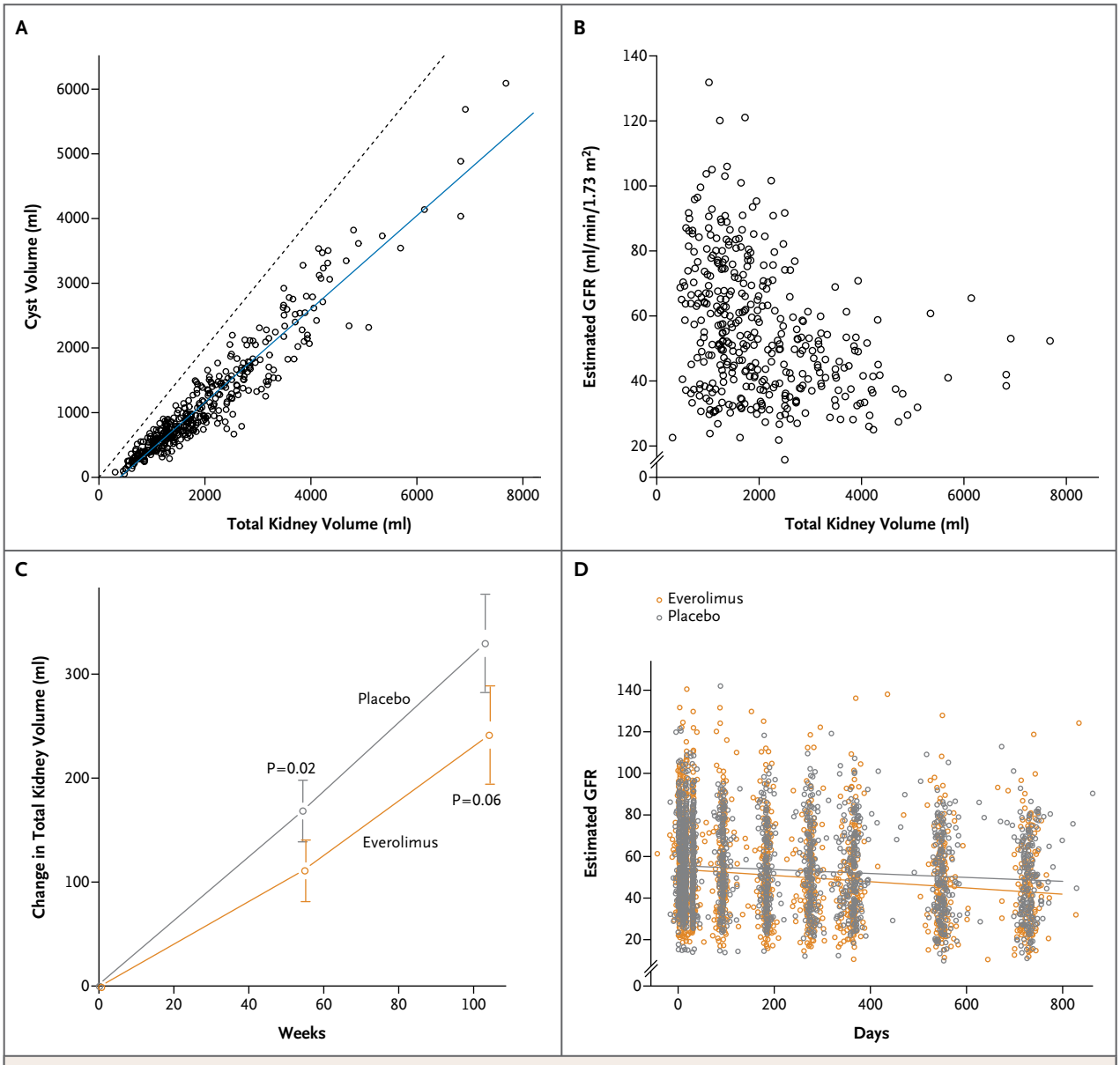

Figure 2. Total Kidney Volume and Other Measures of Renal Function of the Study Patients with Autosomal Dominant Polycystic Kidney Disease.

Panel A shows the correlation (black line) between total kidney and cyst volume in the intention-to-treat population (all patients with at least one post-baseline MRI scan) (r^2=0.92). The dashed line is the line of identity. Panel B shows the correlation between the baseline total kidney volume and the estimated glomerular filtration rate (GFR) in all patients with baseline MRI data and a baseline estimated GFR measurement. Panel C shows the changes in total kidney volume in the intention-to-treat population, with a greater increase with placebo than with everolimus after 12 months (P=0.02) and 24 months (P=0.06). Panel D shows the estimated GFR during the study, with an annual decrement of 5.5 ml per minute per 1.73 m^2 in the everolimus group and 3.5 ml per minute per 1.73 m^2 in the placebo group, based on a linear regression model (P<0.001).

owing to the numbers of patients who left the study prematurely and had missing data for total kidney volume (Table 4 in the Supplementary Appendix). In contrast to a recently published study,[16] in our study, everolimus also slowed the increase in parenchymal volume; the use of computed tomography in that study instead of MRI may explain this difference.

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Table 2. Changes from Baseline in Total Kidney, Cyst, and Parenchymal Volumes in the Intention-to-Treat Population, According to Study Group.*

Volume	Everolimus (N=169)	Placebo (N=177)	Everolimus vs. Placebo (99% CI)	P Value
		milliliters		
Total kidney				
Month 12 change from baseline — mean (99% CI)	102 (60 to 145)	157 (116 to 197)	−54 (−113 to 4)	0.02
Month 24 change from baseline — mean (96% CI)	230 (172 to 288)	301 (248 to 354)	−71 (−149 to 7)	0.06
Cyst				
Month 12 change from baseline — mean (99% CI)	76 (38 to 113)	98 (62 to 134)	−22 (−75 to 30)	0.27
Month 24 change from baseline — mean (96% CI)	181 (133 to 228)	215 (170 to 259)	−33 (−98 to 31)	0.28
Parenchyma				
Month 12 change from baseline — mean (99% CI)	26 (3 to 49)	62 (40 to 84)	−36 (−68 to −5)	0.003
Month 24 change from baseline — mean (96% CI)	56 (21 to 92)	93 (62 to 124)	−37 (−83 to 10)	0.11

* The intention-to-treat population consisted of all patients with at least one post-baseline MRI scan. P values were calculated with the use of analysis of covariance. Missing values were imputed by means of a multiple-scan imputation procedure.[15] CI denotes confidence interval.

Our linear regression model predicted a steep annual decline in the estimated GFR among patients receiving everolimus, owing to the significantly accelerated deterioration in renal function between months 6 and 18. However, the estimated GFR did not differ significantly between the everolimus group and the placebo group at 2 years. The estimated GFR of the everolimus group improved during the first 3 months, before declining over the subsequent months, indicating that linear regression does not optimally model the changes in renal function in patients with ADPKD who are receiving everolimus. Increased mTOR kinase activity is not detectable in all cysts[17,18]; rapid shrinkage of susceptible cysts during the first months of treatment may underlie the unexpected short-term increase in renal function. Since the mTOR kinase cascade supports glomerular hypertrophy and maintains renal function after the loss of renal parenchyma,[19] a possible mechanism of the effect of everolimus is that the drug initially preserves renal function by inhibiting cyst growth and subsequently reverses glomerular hypertrophy and hyperfiltration.[20] Alternatively, the reversal of renal hypertrophy might reduce the GFR and thereby protect kidneys in patients with ADPKD from long-term damage caused by hyperfiltration. Our study was too short to assess such effects.

In addition, the increased rate of peripheral edema and consequent use of diuretics in the everolimus group may have negatively affected renal function. We cannot rule out that mTOR inhibition has differential effects depending on the stage of disease. In patients with advanced cystic disease, it is possible that fibrosis is irreversible and thus unresponsive to therapies that could improve renal function, obscuring potential benefits in patients with ADPKD who have preserved renal function. Thus, future studies need to address the efficacy of mTOR inhibitors in patients with less-advanced disease.

Our results are partially discordant with those of preclinical studies of murine models of polycystic kidney disease. Everolimus treatment in our study confirmed the effect of mTOR inhibitors on kidney size but not function, underscoring the limitations of experimental models. In ADPKD, cyst growth is presumed to promote the destruction of kidney tissue and the loss of renal function.[12-14] However, our results indicate that the slowing of kidney enlargement does not necessarily improve renal function. Thus, total kidney volume is neither a suitable end point for assessing the outcome of therapeutic interventions nor an adequate surrogate marker for renal function in patients with ADPKD who have large kidneys and renal dysfunction, at least within a treatment interval of 2 years.

Table 3. Serious Adverse Events in the Safety Population, According to Study Group.*

Serious Adverse Event	Everolimus (N=214)	Placebo (N=217)	P Value†
	no. of patients (%)		
Any	80 (37.4)	51 (23.5)	0.002
Death	2 (0.9)	1 (0.5)	0.62
Hematopoietic system			
Anemia	37 (17.3)	11 (5.1)	<0.001
Leukopenia	38 (17.8)	6 (2.8)	<0.001
Thrombocytopenia	30 (14.0)	2 (0.9)	<0.001
Gastrointestinal			
Stomatitis or oral ulcer	91 (42.5)	13 (6.0)	<0.001
Diarrhea	51 (23.8)	35 (16.1)	0.05
Gastritis	11 (5.1)	4 (1.8)	0.07
Nausea	20 (9.3)	12 (5.5)	0.15
Vomiting	12 (5.6)	14 (6.5)	0.84
Infection	156 (72.9)	140 (64.5)	0.06
Nasopharyngitis	83 (38.8)	83 (38.2)	0.92
Bronchitis	22 (10.3)	23 (10.6)	1.00
Sinusitis	15 (7.0)	13 (6.0)	0.70
Pneumonia	7 (3.3)	2 (0.9)	0.10
Folliculitis	8 (3.7)	0	0.004
Herpes zoster	7 (3.3)	3 (1.4)	0.22
Tuberculosis on lymph-node examination	1 (0.5)	0	0.497
Urinary tract infection	31 (14.5)	25 (11.5)	0.39
Metabolism			
Hyperlipidemia	28 (13.1)	5 (2.3)	<0.001
Hypercholesteremia	46 (21.5)	8 (3.7)	<0.001
Hypertriglyceridemia	15 (7.0)	8 (3.7)	0.14
New-onset diabetes	7 (3.3)	2 (0.9)	0.10
Skin			
Acne	30 (14.0)	6 (2.8)	<0.001
Angioedema	12 (5.6)	0	<0.001
Other			
Arthralgia	14 (6.5)	5 (2.3)	0.04
Myalgia	17 (7.9)	4 (1.8)	0.003
Myositis	1 (0.5)	0	0.497
Ovarian cyst	12 (5.6)	0	<0.001
Pneumonitis	2 (0.9)	0	0.25
Epistaxis	10 (4.7)	2 (0.9)	0.02
Neoplasm			
Benign	6 (2.8)	5 (2.3)	0.77
Malignant	3 (1.4)	4 (1.8)	1.00
Flank or abdominal pain	53 (24.8)	50 (23.0)	0.74
Peripheral edema	44 (20.6)	20 (9.2)	0.001

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Table 3. (Continued.)

Serious Adverse Event	Everolimus (N = 214)	Placebo (N = 217)	P Value†
	no. of patients (%)		
Weight			
Decreased	14 (6.5)	3 (1.4)	0.006
Increased	3 (1.4)	7 (3.2)	0.34

* The safety population consisted of all patients who received at least one dose of the study medication.
† P values were calculated with the use of Fisher's exact test.

In conclusion, everolimus appears to retard the growth of kidneys in patients with ADPKD but not to slow the decline in progressive renal impairment. The use of everolimus was associated with a high rate of side effects, similar to the rates found with everolimus in patients who have undergone kidney transplantation.

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APPENDIX

Members of the study committees and study team were as follows: **Protocol-development committee** — G. Walz (chair), K.-U. Eckardt, C. Wanner, U. Kunzendorf, W.H. Hörl, H. Pavenstädt, S. Kramer, H. Gschaidmeier, C. May; **Data and safety monitoring board** — G.A. Müller (chair), A. Schwarz, K. Kühn. **Study team** — *Freiburg:* H.P. Neumann, K. Breitenfeldt; *Münster:* V. Busch, B. Otte; *Kiel:* L. Renders; *Erlangen:* B. Schulze, R. Zeltner; *Berlin (Virchow):* U. Frei, M. Gollasch; *Würzburg:* J. Hörl, S. Osiek; *Heidelberg:* M. Zeier; *Berlin (Charité):* H.H. Neumayer; *Regensburg:* C.A. Böger, B.K. Krämer; *Frankfurt:* E. Scheuermann, S. Haack; *Cologne:* S. Elsemann, P. John; *Essen:* G. Augustiniak; *Lübeck:* M. Nitschke, J.C. Ketel; *Homburg/Saar:* H. Köhler, U. Sester; *Hamburg:* R. Stahl; *Vienna:* D. Diarra, G. Sunder-Plassmann; *Innsbruck:* G. Mayer, M Rudnicki; *Linz:* R. Oberbauer; *Brest:* Y. Lemeur; *Paris:* D. Joly; *Grenoble:* P. Zaoui; *Nantes:* J. Dantal; *Toulouse:* D. Chauveau.

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