Effect of Bardoxolone Methyl on Kidney Function in Patients with T2D and Stage 3b–4 CKD

Pablo E. Pergola^a Melissa Krauth^b J. Warren Huff^b Deborah A. Ferguson^b
Stacey Ruiz^b Colin J. Meyer^b David G. Warnock^c

^aRenal Associates, PA, San Antonio, Tex., ^bReata Pharmaceuticals, Inc., Irving, Tex., and ^cUniversity of Alabama at Birmingham, Birmingham, Ala., USA

Key Words

Inflammation • Oxidative stress • Nrf2 • Chronic kidney disease • Bardoxolone • Estimated glomerular filtration rate • Antioxidant inflammation modulator • Type 2 diabetes

Abstract

Background/Aims: Bardoxolone methyl, a novel synthetic triterpenoid, induces Nrf2, a transcription factor known to play a key role in decreasing oxidative stress and the production of pro-inflammatory molecules. **Methods:** This exploratory multi-center, open-label study assessed the clinical activity and safety of bardoxolone methyl in 20 patients with moderate to severe chronic kidney disease and type 2 diabetes. Patients received 25 mg of bardoxolone methyl daily for 28 days, followed by 75 mg daily for another 28 days. **Results:** The study achieved its primary efficacy endpoint, as demonstrated by a significant increase from baseline in estimated glomerular filtration rate (eGFR) of 7.2 ml/min/1.73 m² ($p < 0.001$). Improvements were seen in approximately 90% of patients and showed a dose- and time-dependent increase in eGFR. The eGFR change paralleled a significant

reduction in serum creatinine (–0.3 mg/dl) and blood urea nitrogen (–4.9 mg/dl), along with an increase in creatinine clearance (+14.6 ml/min/1.73 m²), without a change in the 24-hour creatinine excretion rate. Markers of vascular injury and inflammation were improved by treatment with bardoxolone. No life-threatening adverse events or drug-related serious adverse events were reported. **Conclusions:** The results describe an apparent increase in kidney function following relatively short-term treatment with bardoxolone methyl, a promising new agent that warrants placebo-controlled studies to define its long-term effects on renal function.

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Introduction

Multiple studies have demonstrated associations between measures of inflammation and reduced kidney function, as well as mortality, in patients with chronic kidney disease (CKD) [1–9]. Many renal pathogenic stimuli, including angiotensin II, contribute to inflammation

by increasing the production of reactive oxygen species and activating the pro-inflammatory NF- κ B signaling pathway [10]. To date, therapies used to slow progression of CKD have focused on controlling blood pressure by targeting specific components of the renin-angiotensin-aldosterone system. Despite the clear link between inflammation and CKD, interventions that inhibit general inflammatory processes have yet to be developed for this disease. Bardoxolone methyl is a novel synthetic triterpenoid belonging to the antioxidant inflammation modulator class. Antioxidant inflammation modulators potentially induce the antioxidant and cytoprotective transcription factor Nrf2, reduce the pro-inflammatory activity of the IKK- β /NF- κ B pathway, increase the production of antioxidant and reductive molecules, and decrease oxidative stress, thereby restoring redox homeostasis in areas of inflammation [11–17].

Nrf2 activation is suppressed in animal models of CKD [18], and data from animals with genetic deletion of Nrf2 suggest that the transcription factor plays an important role in maintaining the function and structure of the kidney [19–21]. Histological analysis of kidney tissue in Nrf2-knockout mice shows impaired antioxidant activity and increased oxidative damage, including enlarged glomeruli, mesangial cell proliferation, thickening of the glomerular basement membrane, and glomerulosclerosis. Kidney function is compromised in these animals, as evidenced by decreased creatinine clearance and shortened lifespan [21, 22].

Bardoxolone methyl was first advanced into the clinic to assess its anticancer properties. In two phase 1 trials that included 81 oncology patients, bardoxolone methyl reduced serum creatinine levels, with a corresponding improvement in estimated glomerular filtration rate (eGFR). Improvements were more pronounced in a subset of patients with established CKD and were maintained over time in patients who continued on bardoxolone methyl therapy for 5 months. Based on these observed effects and the well-described role of oxidative stress and inflammation in CKD, especially in type 2 diabetes [23], it was hypothesized that bardoxolone methyl could improve renal function in CKD patients with type 2 diabetes. The present work describes the short-term effects of bardoxolone methyl on eGFR and other renal function and injury measures in an open-label study of patients with moderate to severe CKD and type 2 diabetes.

Methods

Patient Population

The study enrolled a total of 20 patients with a diagnosis of type 2 diabetes and a serum creatinine level of 1.3–3.0 mg/dl (115–265 μ mol/l) in women and 1.5–3.0 mg/dl (133–265 μ mol/l) in men, corresponding to an eGFR between approximately 15 and 45 ml/min/1.73 m². Patients with type 1 diabetes, known non-diabetic renal disease, recent history of cardiovascular disease, need for chronic immunosuppressive therapy, or evidence of hepatic dysfunction were excluded from this study. Patients remained on their prior antidiabetic and antihypertensive medication, provided doses were stable for at least 6 and 12 weeks, respectively, prior to study entry.

Study Design

In this multi-center, open-label, phase 2a study, patients were screened and enrolled at two clinical trial sites within the United States. All patients underwent screening and baseline evaluation from day –14 to day –1 prior to study drug administration. Patients returned to the study center for further evaluations on days 7, 15, 28, 35, 42, and 56. All enrolled patients received 25 mg bardoxolone methyl for 28 consecutive days and were to be dose-titrated to 75 mg bardoxolone methyl for 28 additional consecutive days. Bardoxolone methyl was orally administered once daily in the form of 25- and 50-mg white, opaque, hard-gelatin capsules at least 1 h prior to food intake.

In all patients, eGFR was determined at baseline (day –1) and each study visit thereafter; results are presented for the baseline measurements and at study completion on day 56. Urine was collected for 24 h at baseline (day –3 to day –2) and on day 55 to day 56 for albumin-to-creatinine ratio and creatinine clearance measurements. Blood samples were drawn at baseline (day –1) and on day 56 for eGFR and creatinine clearance measurements. Safety was monitored by documenting all adverse events and clinical laboratory tests from days 7, 15, 28, 35, 42, and 56. Biomarkers of biological activity were evaluated in blood and urine at baseline (day –1) and day 56. Compliance was documented by the use of patient diaries, count of study medication remaining at each study visit, and measurement of plasma levels of bardoxolone methyl.

The study was conducted according to Good Clinical Practice guidelines, and protocol approval was obtained from each investigator's institutional review board or independent ethics committee. All participants provided written informed consent.

Endpoints

The primary endpoint was the change from baseline (day –1) to day 56 in eGFR based on the four-variable equation developed by the Modification of Diet in Renal Disease (MDRD) study group [24]. Secondary endpoints were changes from baseline in other parameters of kidney function, including serum creatinine, creatinine clearance, urine albumin-to-creatinine ratio, blood urea nitrogen (BUN), and 24-hour urine creatinine excretion. Various biomarkers of oxidative stress, inflammation, and renal injury were also evaluated as exploratory variables. Circulating endothelial cells (CECs) were analyzed by ApoCell, Inc. (Houston, Tex., USA). Urine N-acetyl- β -D-glucosaminidase (NAG) activity was measured using a modified colorimetric assay (Diazyme Laboratories, Poway, Calif., USA), and urine neutrophil gelatinase-associated lipocalin (NGAL) levels were quantified using

Table 1. Baseline characteristics of 20 enrolled CKD patients with type 2 diabetes

Age, years	64.4 ± 10.6
Median	64.0
Min, max	34, 79
Gender, n (%)	
Male	9 (45)
Female	11 (55)
Ethnicity, n (%)	
Hispanic or Latino	15 (75)
Not Hispanic or Latino	5 (25)
Race, n (%)	
White	18 (90)
Black	2 (10)
Weight, kg	101.5 ± 26.7
95% CI	89.0, 114.0
Median	92.9
Systolic blood pressure, mm Hg	142.8 ± 19.6
95% CI	133.6, 151.9
Median	140.5
Diastolic blood pressure, mm Hg	70.0 ± 11.9
95% CI	64.5, 75.6
Median	69.3
eGFR, ml/min/1.73 m ²	30.3 ± 8.0
95% CI	26.6, 34.1
Median	30.2
Stage 4 CKD, n (%)	10 (50)
Glycosylated hemoglobin, %	7.8 ± 2.2
95% CI	6.8, 8.9
Median	7.3
Duration of diabetes, years	15.5 ± 12.4
Median	11.5
Min, max	0, 48
Diabetic retinopathy, n (%)	4 (20)
Diabetic neuropathy, n (%)	8 (40)
Albuminuria, n (%)	
ACR 0–30 mg/g	7 (35)
ACR >30–300 mg/g	4 (20)
ACR >300 mg/g	9 (45)
Hypertension, n (%)	20 (100)
ACE inhibitor and/or ARB use, n (%)	15 (75)
Insulin use, n (%)	13 (65)
Statin use, n (%)	16 (80)

Plus-minus values are mean ± SD.

CI = Confidence interval of mean; ACR = albumin-to-creatinine ratio.

a sandwich ELISA (Enzo Life Sciences, Plymouth Meeting, Pa., USA). To correct for variability in urine concentration, urine creatinine levels were measured by a colorimetric assay (Enzo Life Sciences) and used to normalize urine NAG and NGAL values.

Safety assessments comprised evaluation of adverse events and regular monitoring of laboratory parameters during treatment, as well as 1 month after treatment ended.

Statistical Analysis

The sample size was generated to satisfy pre-stated conditions for detecting clinically meaningful effects for within-group comparisons. Calculations were made to satisfy requirements for 95% confidence intervals or two-sided tests sized at α levels of 0.05 and powered at 90%. These calculations netted a sample size of 17 patients, which was adjusted to 20 patients to allow for a modest number of non-evaluable patients.

Continuous variables were summarized by the mean ± SD. Summarization of categorical variables was made by use of patient counts and their related percentages. For eGFR and all other efficacy parameters, within-patient changes from baseline to end-of-study were evaluated following 8 weeks. All statistical tests were two-sided with an α level of 0.05.

Results

Patient Disposition

A total of 42 patients were screened for inclusion into the study, 22 of whom did not meet one or more of the inclusion or exclusion criteria. Of the 20 patients who enrolled, 18 (90%) completed the planned 56 days of dosing. Two patients (10%) were withdrawn from the study following approximately 1 week of therapy, after it was determined that they were ineligible by inclusion/exclusion criteria. These patients were included only in baseline assessments.

Of 18 patients, 16 completed the study according to protocol. Two additional patients completed 56 days of study drug therapy but remained on the 25-mg dose. One patient was not escalated to the planned dose of 75-mg due to elevated liver transaminases on day 29, and the other patient was not escalated due to new onset of atrial fibrillation. Three patients had delayed titration, switching to 75-mg treatment on either day 30, 36, or 50, instead of on day 29. The mean duration of treatment in the 20 enrolled patients was 50 days, ranging from 7 to 56 days.

Baseline Characteristics

The average age was 64 years; 55% of the patients were female, and the majority (75%) were Hispanic or Latino (table 1). The mean duration of type 2 diabetes was 15.5 years; 20% of the patients had a history of diabetic retinopathy, and 40% had a history of diabetic neuropathy. Most patients were on antihypertensive medicine (80%), statins (80%), ACE inhibitors and/or ARBs (75%), and insulin (65%). The mean eGFR was 30.3 ml/min/1.73 m² at baseline. Thirteen patients (65%) had some degree of albuminuria, including 9 (45%) who had an albumin-to-creatinine ratio >300 mg/g.

Table 2. Summary of eGFR values

	Baseline	Day 56	Change ^a
n	20	18	18
Mean $\pm$ SD, ml/min/1.73 m ²	30.3 $\pm$ 8.0	38.0 $\pm$ 8.2	+7.2 $\pm$ 5.3
95% CI	26.6, 34.1	33.9, 42.0	4.6, 9.9
Median (IQR)	30.2 (23.0, 35.5)	39.0 (33.4, 42.9)	+5.5 (3.1, 11.5)
p value ^b	–	–	<0.001 [†]

CI = Confidence interval of mean; IQR = interquartile range.

^a Day 56 minus baseline.

^b p value reported for mean change from baseline and calculated from two-sided paired t tests; [†] indicates significant change from baseline.

Fig. 1. Mean eGFR over time is shown for all patients (n = 18) treated with bardoxolone methyl for 56 days; error bars represent SEM. Statistical analysis of the change in eGFR from baseline was performed on day 28 and day 56. [†] p = 0.004; ^{††} p < 0.001.

Fig. 2. Individual eGFR changes from baseline following 56 days. Changes shown for all patients (n = 18) treated with bardoxolone methyl for 56 days. Asterisks indicate patients who did not have their doses escalated to 75 mg/day.

Primary Efficacy Analysis

The study successfully achieved its primary efficacy endpoint, as demonstrated by a large, significant increase in eGFR at day 56 compared to the baseline values (table 2). The improvement in eGFR occurred steadily over the 2-month period (fig. 1). The change was statistically significant after the initial 4 weeks of treatment with 25 mg bardoxolone methyl (2.8 ml/min/1.73 m², p = 0.004) and was increased further by an additional 4 weeks of treatment, during which most patients received 75 mg bardoxolone methyl (7.2 ml/min/1.73 m², p < 0.001). Improvements were consistent across patients, with 16 of 18 patients (89%) experiencing an increase in eGFR throughout the duration of the study (fig. 2).

Markers of Renal Function and Creatinine Handling

Serum creatinine decreased at day 56 by 0.3 mg/dl from a baseline mean of 2.0 mg/dl (p < 0.001), with no corresponding change in 24-hour urinary creatinine excretion (table 3). There was also a significant increase in the calculated creatinine clearance at day 56 (+14.6 ml/min/1.73 m², p = 0.006).

BUN was reduced by −4.9 mg/dl (p = 0.05), and Pearson's statistics showed a significant correlation between the change in BUN and change in eGFR (coefficient of −0.66, p = 0.003), consistent with an improvement in renal function. There was no change detected in the median urine albumin-to-creatinine ratio (p = 0.65).

Table 3. Summary of renal and inflammation markers at baseline and change at day 56

	Baseline	Day 56	Change ^a	p value ^b
<i>Renal markers</i>				
Serum creatinine, mg/dl	2.0 ± 0.3	1.7 ± 0.3	−0.3 ± 0.3	<0.001 [†]
Creatinine clearance ^c , ml/min/1.73 m ²	36.4 ± 10.7	51.2 ± 19.4	+14.6 ± 18.9	0.006 [†]
Urine albumin/creatinine ratio ^c , µg/mg	160.0 (28.4, 463.5)	194.6 (41.3, 464.5)	+32.1 (7.4, 57.8)	0.65
Blood urea nitrogen, mg/dl	37.6 ± 12.1	31.2 ± 10.0	−4.9 ± 10.0	0.05
24-hour urine creatinine excretion ^d , mg/24 h	1,272.1 ± 452.7	1,333.5 ± 440.6	+62.9 ± 353.5	0.47
<i>Inflammation markers</i>				
Circulating endothelial cells ^e , CD105+/ml	5.3 ± 3.0	3.5 ± 1.7	−1.9 ± 2.5	0.007 [†]
Circulating endothelial cells ^e , CD105+ and iNOS+/ml	2.9 ± 1.4	1.0 ± 1.0	−1.9 ± 1.8	0.001 [†]
Urine NGAL ^{f,h} , ng/mg creatinine	79.0 ± 98.8	93.2 ± 112.5	+4.0 ± 145.8	0.93
Urine NAG ^{g,h} , IU/g creatinine	15.7 ± 9.6	16.8 ± 6.4	+0.5 ± 7.2	0.83

Baseline and change values represented as mean ± SD for all except urinary ACR, shown as median (IQR). n = 20 and 18 for baseline and day 56/change, respectively, unless otherwise noted.

^a Day 56 minus baseline. ^b p values calculated from two-sided paired t tests; [†] indicates significant change from baseline. ^c Baseline (n = 19), day 56 (n = 18), and change (n = 17); median (25th

percentile, 75th percentile). ^d Baseline (n = 19), day 56 (n = 17), and change (n = 17). ^e Baseline (n = 16), day 56 (n = 17), and change (n = 16). ^f Baseline (n = 14), day 56 (n = 16), and change (n = 12). ^g Baseline (n = 12), day 56 (n = 15), and change (n = 10). ^h Normalized for urine creatinine.

Markers of Renal Injury, Inflammation, and Oxidative Stress

CECs, markers of endothelial dysfunction and vascular injury, were significantly decreased on day 56 by 28% (p = 0.007). The inflammatory status of CECs was also measured by inducible nitric oxide synthase (iNOS) expression, which was significantly decreased by 46% (p = 0.001). No increases were observed in urinary markers of renal injury, including NGAL and NAG, normalized by urine creatinine concentration.

Blood Pressure and QTc Interval

There were no significant changes from baseline in either diastolic (−0.6 mm Hg, p = 0.73) or systolic (−6.2 mm Hg, p = 0.12) blood pressure. No correlation between eGFR change and blood pressure change was observed. Analysis of QTc data (not shown) also revealed no difference from baseline at day 56.

Safety

There were no life-threatening adverse events, and drug-related adverse events were mild to moderate in severity. Overall, 18 of the 20 patients (90%) reported at least one adverse event. The most common adverse events regardless of attribution to study drug were muscle spasms (n = 7; 35%), chills (n = 3; 15%), and cough (n = 3; 15%) (table 4). Fourteen events occurring in 11 of the pa-

Table 4. Adverse events reported by ≥10% of 20 patients treated with bardoxolone methyl, n (%)

Cardiovascular	
Atrial fibrillation	2 (10)
Hypertension	2 (10)
Peripheral edema	2 (10)
Gastrointestinal	
Nausea	2 (10)
General	
Chills	3 (15)
Fatigue	2 (10)
Pyrexia	2 (10)
Infections	
Nasopharyngitis	2 (10)
Urinary tract infection	2 (10)
Investigations	
Liver function test abnormal	2 (10)
Metabolism and nutrition	
Anorexia	2 (10)
Hyperkalemia	2 (10)
Musculoskeletal and connective tissue	
Muscle spasms	7 (35)
Respiratory, thoracic and mediastinal disorders	
Cough	3 (15)
Rhinorrhea	2 (10)
Skin and subcutaneous tissue	
Rash	2 (10)

tients (55%) were deemed at least possibly related to study medication and included muscle spasms (4 reports, all mild), abnormal liver function tests (2 reports, one mild and one moderate), hypoglycemia (2 reports, mild), nausea (1 report, moderate), anorexia (1 report, mild), decreased appetite (1 report, mild), muscular weakness (1 report, mild), pain in extremity (1 report, mild), and hypogeusia (1 report, mild). One patient reported two serious adverse events of atrial fibrillation (moderate severity) and pleural effusion (moderate severity), which were both deemed unrelated to study medication. No patient was withdrawn from the study due to an adverse event, although two patients were not dose-titrated as a result of adverse events.

Modest, asymptomatic increases in alanine transaminase and aspartate transaminase that followed a consistent pattern were noted in almost all patients upon initiation of treatment, with mean values peaking by day 15. A single patient experienced elevations that were more than twice the upper limit of normal. Elevations resolved to levels less than the upper limit of normal in almost all patients within 2 weeks after peaking, while patients continued on study drug, and did not recur once resolved. Concurrent significant decreases in serum bilirubin were noted from a mean baseline of 0.6 mg/dl (-0.1 mg/dl, $p < 0.005$), and no changes were noted in serum lactic dehydrogenase.

Discussion

This exploratory study employed an open-label, single-arm design to profile the activity and safety of bardoxolone methyl. Patients in the trial were typical of the population with CKD and type 2 diabetes, regarding age, duration and severity of diabetes, treatment status, and the prevalence of comorbidities. All patients had moderate to severe CKD, with 50% each having stage 3 or stage 4 disease, and the majority had significant albuminuria. Furthermore, patients in the study were receiving standard care for CKD and diabetes, with 75% treated with an ACE inhibitor or ARB. Treatment with bardoxolone methyl in this setting resulted in a notable increase in mean eGFR of 7.2 ml/min/ 1.73 m² over an 8-week period from a mean baseline of 30.3 ml/min/ 1.73 m².

The increase in eGFR observed in this study paralleled measured increases in creatinine clearance, without a change in the 24-hour creatinine excretion rate, suggesting that the decrease in serum creatinine was not

a consequence of a decrease in creatinine production. In the steady state, these results could be attributed to a relative increase in tubular creatinine secretion. Direct measurements of GFR in human subjects are needed to better characterize the effect of bardoxolone methyl on renal function; however, preclinical studies support the interpretation that GFR was increased by bardoxolone methyl. A study in cynomolgus monkeys demonstrated that the effects were independent of tubular secretion, as administration of cimetidine, an agent known to inhibit secretion of creatinine by the proximal tubules, did not abrogate the reductions in serum creatinine in response to bardoxolone methyl [S. Ruiz, PhD, unpubl. data].

There were no major protocol-related adverse events reported in patients treated with bardoxolone methyl. Muscle spasms and increases in transaminases appeared to be drug-related. The mechanism for muscle spasms may be associated with induction of Nrf2, which is known to improve insulin sensitivity and significantly increase glucose uptake [25–27]. Changes in transaminases are likely the result of Nrf2-mediated transaminase gene transcription [28–30]. Transaminase increases were not accompanied by increased bilirubin levels or evidence of liver toxicity. Available data in transgenic mouse models of Nrf2 activation suggest that this phenotype associated with Nrf2 induction (increase in transaminases with either no change or a decrease in serum bilirubin) does not adversely affect the liver [28]. Similar increases in transaminases in the absence of bilirubin increases have also been observed in other clinical trials with bardoxolone methyl. This effect has also been observed in cynomolgus monkeys treated with bardoxolone methyl for 12 months and was not associated with adverse liver histopathology [C.J. Meyer, MD, unpubl. data].

Increased CECs have been shown to correlate directly with endothelial dysfunction and increased cardiovascular and renal disease, as well as hypertension [1, 31–33]. The reduction in CECs observed in this study indicates the potential for reduced vascular damage and improved inflammatory status within the vasculature, as indicated by even larger reductions in CECs that stain positive for iNOS activity. The lack of change in urinary NGAL and NAG concentration is also consistent with the lack of any nephrotoxic effect attributable to treatment with bardoxolone methyl [34, 35].

The current phase 2a open-label study has several important limitations. The lack of a placebo control group and non-random allocation of all patients to the treatment group limit the applicability of the results and in-

terpretation of adverse response rates. Also, the results reported herein only describe an improvement in markers of kidney function following relatively short-term treatment with bardoxolone methyl. The possibility that the observed increases in eGFR could further exacerbate the underlying disease process, thereby promoting rather than delaying progression of CKD, is another potential concern. These questions must be addressed in prospective randomized, placebo-controlled, longer term studies that will assess whether this effect is maintained and leads to improved renal outcomes, including delayed progression to end-stage renal disease.

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