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Neeraj Dhaun, Iain M. MacIntyre, Debbie Kerr, Vanessa Melville, Neil R. Johnston, Scott Haughie, Jane Goddard and David J. Webb

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Abstract—Proteinuria is associated with adverse cardiovascular and renal outcomes that are not prevented by current treatments. Endothelin 1 promotes the development and progression of chronic kidney disease and associated cardiovascular disease. We, therefore, studied the effects of selective endothelin-A receptor antagonism in proteinuric chronic kidney disease patients, assessing proteinuria, blood pressure (BP), and arterial stiffness, key independent, surrogate markers of chronic kidney disease progression and cardiovascular disease risk. In a randomized, double-blind, 3-way crossover study, 27 subjects on recommended renoprotective treatment received 6 weeks of placebo, 100 mg once daily of sitaxsentan, and 30 mg once daily of nifedipine long acting. Twenty-four–hour proteinuria, protein:creatinine ratio, 24-hour ambulatory BP, and pulse wave velocity (as a measure of arterial stiffness) were measured at baseline and week 6 of each treatment. In 13 subjects, renal blood flow and glomerular filtration rate were assessed at baseline and week 6 of each period. Compared with placebo, sitaxsentan reduced 24-hour proteinuria (−0.56±0.20 g/d; P=0.0069), protein:creatinine ratio (−38±15 mg/mmol; P=0.0102), BP (−3.4±1.2 mm Hg; P=0.0069), and pulse wave velocity (−0.64±0.24 m/s; P=0.0052). Nifedipine matched the BP and pulse wave velocity reductions seen with sitaxsentan but did not reduce proteinuria. Sitaxsentan alone reduced both glomerular filtration rate and filtration fraction. It caused no clinically significant adverse effects. Endothelin-A receptor antagonism may provide additional cardiovascular and renal protection by reducing proteinuria, BP, and arterial stiffness in optimally treated chronic kidney disease subjects. The antiproteinuric effects of sitaxsentan likely relate to changes in BP and renal hemodynamics. (Hypertension. 2011;57:772-779.)  ● Online Data Supplement

Key Words: endothelin ■ proteinuria ■ blood pressure ■ arterial stiffness ■ chronic kidney disease

Chronic kidney disease (CKD) is common, affecting 6% to 11% of the population globally.1 It is strongly associated with incident cardiovascular disease (CVD).2 Proteinuria is a common feature of CKD, and the degree of proteinuria is closely associated with renal outcome and cardiovascular events.3 Importantly, a reduction in proteinuria is associated with a slowing of both the decline in glomerular filtration rate (GFR)3 and the progression to end-stage renal disease.3 In addition, proteinuria reduction is associated with an improved cardiovascular outcome in both those with4 and without5 CKD. Thus, a reduction in proteinuria to a greater extent than accounted for by BP-lowering alone.8 Nevertheless, many CKD patients have significant residual proteinuria despite optimal treatment.9 Hypertension is a frequent finding in patients with CKD,10 and despite treatment with multiple antihypertensive agents, the majorit of CKD patients fail to reach target BP.11 In addition to hypertension and proteinuria, arterial stiffness12 makes an important contribution to CVD risk in CKD. Thus, there remains an unmet need for newer treatments in CKD that will not only lower proteinuria and BP beyond the levels achieved with standard therapies but also have favorable effects on arterial stiffness and so offer longer-term cardiovascular and renal protection.

Endothelin (ET) 1 is implicated in both the development and progression of CKD.13 ET-1 also contributes to arterial stiffness in patients with CKD.14 The effects of ET-1 are
mediated via 2 receptors, the ET_4 and ET_6 receptors, with the major pathological effects in CKD being ET_4 receptor mediated. However, there are currently few human studies in CKD. The aim of the current study was to evaluate whether the oral ET_4 receptor antagonist, sitaxsantan, is able to reduce proteinuria, BP, and arterial stiffness longer term in subjects with chronic nondiabetic proteinuric kidney disease.

Methods

Subjects
We enrolled subjects 18 to 70 years of age with stable CKD stages 1 to 4 and proteinuria (>300 mg/d). Subjects were on treatment with ACE inhibitors and/or ARBs (but not necessarily diuretics) for their proteinuria. Explicitly, doses of one or both of drugs were titrated to the maximum tolerated, dependent on BP, renal function, serum potassium levels, and adverse effects. All of the medications were unchanged over the 3 months preceding the studies.

Patients with significant comorbidity, including diabetes mellitus, heart or lung disease, and peripheral vascular disease, were excluded. To enhance homogeneity and avoid other influences on vascular reactivity, patients with vasculitis, other systemic inflammatory disease, polycystic kidney disease, and nephrotic syndrome were excluded. Furthermore, we excluded patients with abnormal liver enzymes, hemoglobin <8 g/dL, and women of childbearing potential.

Thirty-three patients with stable proteinuric CKD were screened, and 27 were recruited into the studies. These were performed between June 2007 and March 2009 in the University of Edinburgh Clinical Research Centre with the approval of the local research ethics committee and the written informed consent of each subject. The investigations conformed to the principles outlined in the Declaration of Helsinki.

Study Protocol
This was a single-center, 3-phase randomized, double-blind, placebo-controlled crossover study. Its purpose was to investigate the safety, tolerability, and efficacy of 100 mg of sitaxsantan once daily versus placebo on reduction of proteinuria (primary end point), BP, and arterial stiffness (secondary end points) in subjects with CKD. Because previous studies with ET receptor antagonists have shown a reduction in BP and BP reduction may contribute to changes in protein excretion and arterial stiffness, 30 mg of nifedipine long acting (LA) once daily was used as an open-label active control. Our choice of active control agent was based, most importantly, on clinical considerations. However, data from a previous study using an ET_4 receptor antagonist administered to 22 subjects in a crossover design reported a reduction in proteinuria of up to ~496 μg/mg with a SE of 141 μg/min. This is ~0.7 g/dl with an SD of 0.9 g/dl. Using these data, it is possible to show that the current study size would have 80% power to detect such a difference at the 2-sided 5% significance level. Of the 30 subjects to be enrolled in the main study, the aim was for 24 subjects to complete and ~15 subjects were to be included in the substudy, with the aim of 12 subjects completing that. Similar calculations demonstrate that the substudy had ~50% power to detect statistically significant changes, but the substudy was exploratory in nature, with the principal aim of examining trends in the data.

For efficacy end points, the changes from baseline to week 6 and from baseline to week 3 were analyzed using a mixed model with repeated measures. The model was implemented using PROC MIXED in SAS with terms for treatment group (fixed effect, categorical variable), baseline value (fixed effect, continuous variable, as appropriate for the end point), period effect (fixed effect, categorical variable), week (the “repeated” effect), week-by-treatment interaction, and subject-by-period interaction (the “subject” blocking effect). The model was fitted using restricted maximum likelihood estimation, and an autoregressive covariance structure was implemented. Least squares means estimates for each treatment and the treatment differences (100 mg of sitaxsantan minus placebo; 100 mg of sitaxsantan minus 30 mg of nifedipine LA, and 30 mg of nifedipine LA minus placebo) were generated for weeks 3 and 6 from the treatment group-by-week interaction. Associated SEMs and P values were calculated. The assumptions of the model were checked by investigation of a normal probability plot of standardized residuals and a plot of standardized residuals versus fitted values. Carryover and sequence effects were explored by adding these terms into the model (and removing if nonsignificant). In addition, all of the data were summarized using simple summary statistics (observed means, medians, and SDs). Percentage changes were summarized for each treatment. Median differences between treatments were calculated, and 95% CIs for the differences were derived using the Hodges-Lehman estimator.

For the renal substudy, GFR and effective renal plasma flow were calculated from inulin and para-aminoinhippurate sodium clearances, respectively. Effective renal blood flow (ERBF) was calculated by dividing effective renal plasma flow by 1−(hematocrit), and effective renal vascular resistance by dividing MAP by ERBF. Effective filtration fraction (EFF) was defined as GFR/ERBF.
Role of the Funding Source
This study was designed by the academic authors. The sponsor was responsible for generating the subject randomization schedule, gathering the data from the investigational site to create the clinical database, and for data unblinding. On the basis of an analysis plan developed in collaboration with the academic authors, who also took responsibility for interpretation of the data and for submitting this article for publication, the sponsor did the data analysis. All of the authors had full access to study results after unblinding the data.

Results
All 27 of the subjects completed all 3 phases of the study. Patient diagnoses were IgA nephropathy (n=14; 52%), focal segmental glomerulosclerosis (n=6; 22%), membranous nephropathy (n=3; 11%), hypertensive nephrosclerosis (n=2; 7%), reflux nephropathy, and microhematuria of presumed glomerular origin (n=1; 4%, for both), and 1 subject had an unknown cause for his or her CKD. Subject baseline parameters are shown in Table 1. For all of the subjects, baseline parameters did not differ among the 3 study phases.
Sitaxsentan Versus Placebo

Proteinuria

Placebo was associated with no significant changes in 24-hour urinary protein excretion or protein:creatinine ratio (PCR) from baseline to week 3 or week 6. Sitaxsentan, however, significantly reduced both 24-hour proteinuria and PCR by $\approx 30\%$ by study end (Figure 1). These effects of sitaxsentan on proteinuria were apparent at week 3 of the study period. The observed means (±SD) for 24-hour proteinuria were 2.07±1.77 g/d at baseline and 1.34±1.16 g/d at week 6. For PCR these were 156±147 and 109±109 mg/mmol. For 24-hour proteinuria, the least squares mean changes (±SEM) at week 6 were $-0.73±0.14$ g/d for sitaxsentan and $0.09±0.14$ g/d for placebo ($P=0.0001$). For PCR, these were $-48±10$ and $8.6±10$ mg/mmol ($P=0.0002$).

Sitaxsentan reduced proteinuria by $\approx 25\%$ in 19 (70%) of 27 subjects and by $\approx 40\%$ in 9 (33%) of 27 subjects. Only 2 subjects failed to show a reduction in 24-hour urine protein excretion and only 1 in PCR. Furthermore, the degree of proteinuria reduction closely related to the baseline urinary protein excretion, with subjects with higher baseline proteinuria achieving a greater reduction ($r^2=0.67; P<0.01$). This effect was seen across all levels of GFR (data not shown).

BP and Arterial Stiffness

Although placebo did not significantly affect MAP, systolic BP, or diastolic BP between baseline and week 6 of the study period, sitaxsentan reduced all 3 of the parameters by $\approx 5$ mm Hg after 3 and 6 weeks dosing (Figure 2).

Placebo had no significant effects on PWV or cAlx over the 6-week study period, whereas sitaxsentan reduced both by study end. PWV fell by $\approx 5\%$ compared with baseline, a difference of $\approx 8\%$ compared with placebo (Hodges-Lehman 95% CI: $-16\%$ to $-2\%$; Figure 3).
Sitaxsentan Versus 30 mg of Nifedipine LA
After 6 weeks of dosing there were no significant differences between sitaxsentan and nifedipine in the reductions from baseline in BP parameters. Systolic BP was reduced by $-4.3\pm1.2$ versus $-4.4\pm1.2$ mm Hg, diastolic BP by $-3.7\pm0.8$ versus $-2.7\pm0.8$ mm Hg, and MAP by $-3.9\pm0.9$ versus $-3.4\pm0.9$ mm Hg (least squares mean±SEM for sitaxsentan and nifedipine, respectively). Despite this, sitaxsentan reduced proteinuria to a significantly greater extent than nifedipine and nifedipine, respectively. Although GFR was similar at day 0 and week 6 with placebo, sitaxsentan, or nifedipine. Although GFR was similar at day 0 and week 6 with placebo, sitaxsentan, or nifedipine. Although GFR was similar at day 0 and week 6 with placebo, sitaxsentan, or nifedipine.

Renal Substudy
ERBF did not change from day 0 to week 6 with placebo, sitaxsentan, or nifedipine. Although GFR was similar at day 0 and week 6 with placebo and nifedipine, sitaxsentan produced a substantial fall in GFR by week 6. EFF remained unchanged between day 0 and week 6 with both placebo and nifedipine. However, EFF was lower with sitaxsentan. This was a consistent finding, with 12 of 13 subjects demonstrating a fall in EFF ($n=13$; Table 2 and Figure 4). Ten subjects had an EFF of $>20\%$ at baseline. These subjects showed a fall of $>2\%$ (range: 2.1% to 8.9%) after 6 weeks of sitaxsentan treatment. The 3 subjects with an EFF $<20\%$ at baseline showed less impressive reductions in EFF after sitaxsentan dosing. All of the changes in renal hemodynamics had returned to baseline before starting the next phase of the study (minimum 2 weeks).

Adverse Events
There was no difference in the overall incidence of adverse events between the sitaxsentan and placebo groups (Table 3). Of note, there was no significant weight gain (see Figure S1), fall in hemoglobin or hematocrit, or rise in serum potassium associated with sitaxsentan treatment compared with placebo.

Discussion
We have demonstrated that sitaxsentan, an oral selective ET$_A$ receptor antagonist, reduces proteinuria, BP, and arterial stiffness in patients with proteinuric nephropathy. These effects were seen in patients already receiving optimal treatment with ACE inhibitors and ARBs and were at least in part BP independent. These findings suggest a potential role for ET$_A$ receptor antagonism in conferring longer-term cardiovascular and renal benefits in patients with CKD.

Proteinuria reduction is important both for reducing risk of CKD progression and associated CVD. However, despite maximum achievable renin-angiotensin system blockade, many patients with proteinuric CKD have significant residual proteinuria. In the current study all of the subjects were established on maximally tolerated treatment with ACE inhibitors and ARBs. Individually, proteinuria is reduced with ET$_A$ receptor antagonists, but the magnitude of this reduction may be insufficient to prevent CKD progression. Current studies with ET$_A$ receptor antagonists should focus on the potential to further reduce proteinuria and prevent CKD progression in patients already receiving optimal treatment with ACE inhibitors and ARBs.
inhibitors and/or ARBs with good BP control. Despite this, mean baseline proteinuria was still significant at ~2 g/d (range: 0.3 to 7.8 g/d). Importantly, the data presented here support a potential role for ET receptor antagonists as a novel class of drug to help further reduce proteinuria in these patients on top of standard therapy. This should have the capacity to reduce CKD progression and the associated CVD, morbidity, and mortality.

Interactions between the ET and renin-angiotensin systems are well established. Furthermore, we have shown recently that acute ETₐ receptor antagonism can reduce proteinuria by an additional ~30% on top of that achieved with optimal treatment with inhibitors of the renin-angiotensin system in subjects with proteinuric CKD. The current study suggests that these effects are maintained longer term and are of a similar magnitude. Interestingly, the size and time course of this effect are similar to those seen with blockers of the renin-angiotensin system. Furthermore, of those subjects showing ~40% reduction in urinary protein leak (9 of 27), 4 were on dual ACE inhibitor/ARB therapy, supporting a role for ET receptor antagonists as adjunctive treatments for CKD patients already established on renin-angiotensin system inhibitors. As has been shown previously with ACE inhibitors, the reduction in proteinuria was related to baseline proteinuria, with subjects with a higher level of baseline urinary protein leak achieving greater reductions. This effect was seen across the range of renal function studied.

The effects of sitaxsentan on proteinuria described here are likely explained by changes in both systemic and renal hemodynamics. As expected, there was a correlation between the reductions in BP and proteinuria after 6 weeks of sitaxsentan dosing ($r^2=0.16; P=0.04$). However, sitaxsentan also reduces proteinuria through BP-independent effects. Other longer-term targets for selective ETₐ receptor antagonism include the podocyte, which has been implicated in the development of proteinuria. In a recent study, the ET receptor antagonist atrasentan reduced macroalbuminuria in subjects with diabetic nephropathy in the absence of a change in BP. In the current study, our active control nifedipine matched the fall in BP seen with sitaxsentan, but despite this, sitaxsentan reduced proteinuria to a greater degree. Furthermore, for the reduction in BP seen with sitaxsentan (~4 mm Hg) a less impressive fall in proteinuria than the observed at ~30% would be expected. ACE inhibitors that reduce proteinuria by a similar degree to the effect seen here with sitaxsentan have more impressive effects on BP, reducing it by ~10 mm Hg.

Our substudy data support a renal hemodynamic mechanism for the reduction in proteinuria seen with sitaxsentan. ETₐ receptor antagonism had no effect on renal blood flow or renal vascular resistance. However, as in previous studies, there was a very consistent fall in filtration fraction (~4%), suggesting that ET-1 induces an ETₐ receptor-mediated preferential efferent arteriolar constriction. These effects are analogous to, and occur in addition to, those seen with renin-angiotensin system blockade. This postulated reduction in efferent arteriolar tone with ETₐ receptor antagonism should reduce glomerular perfusion pressure. This will result in a reduction in proteinuria with an associated short-term fall in GFR. Consistent with this proposed effect, we observed a significant fall in GFR (~9 mL/min) after 6 weeks of sitaxsentan treatment. In patients already prescribed blockers of the renin-angiotensin system, these effects, despite an initial fall in GFR, should correlate with longer-term slowing of the rate of CKD progression.

The current study confirms the concept that blocking the ETₐ receptor reduces BP in CKD. Sitaxsentan reduced BP modestly (a fall in MAP of ~4 mm Hg). This effect may have been more impressive had the subjects not had such good baseline BP control. Previous studies of the longer-term antihypertensive effects of ET receptor antagonism suggest that both selective ETₐ and mixed ETₐ/B antagonists are effective at reducing BP in untreated hypertensive patients or those with resistant hypertension. Our current data suggest that, at least in patients with CKD, where BP control is often difficult, ET receptor antagonism may provide a novel strategy to lower BP to a greater extent than that achieved with existing treatments.

Sitaxsentan also significantly improved arterial stiffness as measured by PWV and cAIx compared with placebo. This is likely to be attributable largely to the reduction in BP seen with sitaxsentan. Interestingly, despite similar BP effects, sitaxsentan reduced cAIx to a greater extent than nifedipine. In the current study, unlike for BP and proteinuria, the reductions in PWV and cAIx were higher at 6 weeks than after 3 weeks of sitaxsentan treatment. It is possible that longer treatment with an ETₐ receptor antagonist might reduce PWV further and perhaps to a greater degree than nifedipine. There are few clinical trials demonstrating that differential lowering of PWV with medical treatment results in different cardiovascular or renal outcomes, but the importance of such studies is underscored by epidemiological data, suggesting that PWV is an independent risk factor for CVD morbidity and mortality.

Six weeks of sitaxsentan dosing in subjects with varying degrees of proteinuric CKD was not associated with any more adverse events than placebo. Importantly, we observed no weight gain, clinically significant edema, fall in hemoglobin.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=27)</th>
<th>Sitaxsentan (n=27)</th>
<th>Nifedipine (n=27)</th>
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</thead>
<tbody>
<tr>
<td>Adverse events, n</td>
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<td>15</td>
<td>32</td>
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<tr>
<td>Subjects with adverse events, n (%)</td>
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<td>Any serious adverse events, n (%)</td>
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<td>0 (0)</td>
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<tr>
<td>Adverse events reported &gt;5%, n (%)</td>
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<tr>
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<td>1 (4)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Flushing</td>
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<td>1 (4)</td>
<td>2 (7)</td>
</tr>
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<tr>
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<td>2 (7)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Sitaxsentan</td>
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<td>(n=27)</td>
<td>(n=27)</td>
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or hematocrit, or rise in serum potassium. Furthermore, the changes in renal hemodynamics were not associated with sodium retention (data not shown). Fluid retention has been observed in several trials with ET receptor antagonists, although its mechanism remains unclear. ET-1 acts in the renal tubule via the ET₄ receptor to promote natriuresis and diuresis. Thus, edema could be aggravated by mixed ET₂/β antagonists, and its absence in the current study may be explained by the selective ET₂ blocking nature of our drug. In addition, the careful selection of our subjects, excluding those with clinically apparent CVD and overt heart failure (and, thus, a propensity to fluid overload), may also help. From a renal perspective, the lack of rise in serum potassium with sitaxsentan is clinically significant, because this is a troublesome adverse effect with both ACE inhibitors and ARBs limiting their use.

Perspectives
We recognize some limitations to the current work. The study was crossover by design. This may lead to subjects dropping out, limiting its power, as well as having the issue of carryover effects between different treatment phases. However, carryover was not a significant factor in the statistical analysis, and the results from the main study clearly indicate that the power was adequate. Subjects were optimized for treatment of their proteinuria with ACE inhibitors and ARBs but were not necessarily prescribed diuretics. These may potentiate the antiproteinuric effects of renin-angiotensin system blockade. Thus, the current data apply only to those subjects not taking diuretics. Furthermore, although the small study number is reasonable to show benefits of treatment, much larger studies are required to highlight potentially important but infrequent adverse events. In summary, the current data support a role for selective ET₂ receptor antagonism as a novel and worthwhile therapeutic target in CKD to lower proteinuria, BP, and arterial stiffness on top of standard treatment, and on this basis, larger and longer-term studies are now justified.

Addendum
Sitaxsentan has been voluntarily withdrawn by Pfizer, Ltd due to unacceptable side effects. However, the findings in this manuscript remain true for selective endothelin A receptor antagonism.

Acknowledgments
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Disclosures
N.D., I.M.M., J.G., and D.J.W. have all received research grants from Pfizer. N.D. and J.G. have held academic research fellowships funded by educational grants from Pfizer. J.G. and D.J.W. have acted as consultants to Pfizer. S.H. is an employee of Pfizer.

References


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Supplementary material- Figure S1

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Running title: Endothelin antagonism & CKD
Registration number at www.clinicalTrials.gov: NCT00810732
Supplemental Figure 1.

Regular medications including ACE-I and ARB continued

+ 

Sitaxsentan 100mg, Nifedipine LA 30mg or placebo as per randomization

Washout

≥ 2 weeks

Baseline
- 24h BP
- 3 x 24h urine
- Arterial stiffness

Week 3
- 24h BP
- 3 x 24h urine
- Arterial stiffness

Week 6
- 24h BP
- 3 x 24h urine
- Arterial stiffness

Safety data obtained at baseline, week 1, 2, 3, 4 & 6