# Can Pentoxifylline be used as Adjunct Therapy to ACE Inhibitors and ARBs in Preserving Kidney Function?

Cody Carson[1], Akram Al-Makki[2], Brian Shepler[1]

[1]Purdue University College of Pharmacy, West Lafayette, IN, USA; [2]Indiana University Health Arnett Nephrology, Lafayette, IN, USA.

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**ABSTRACT - Purpose.** To determine if there is sufficient evidence to recommend the addition of pentoxifylline to standard ACE inhibitor and ARB therapy in chronic kidney disease patients to reduce proteinuria and preserve kidney function. **Methods**: A search of the literature was conducted using the PubMed.gov and ClinicalTrials.gov search engines and the search terms "pentoxifylline renoprotection", "pentoxifylline CKD", and "pentoxifylline nephropathy". Results were limited to studies in human subjects and published in the English language. No date range was specified. Studies focused on the effects of pentoxifylline on drug induced nephropathy were excluded. **Results**: Nine relevant articles were retrieved and evaluated. The two main populations studied were patients with chronic kidney disease (CKD) and patients with CKD and comorbid type 2 diabetes. Six of the nine studies reported a significant reduction in proteinuria in pentoxifylline treated patients. Four studies reported a significant change in estimated glomerular filtration rate (eGFR). **Conclusion**: Addition of pentoxifylline to ACE inhibitor and ARB therapy may improve proteinuria in CKD patients. There is conflicting evidence as to whether pentoxifylline will improve kidney function as measured by eGFR.

**Key words**: pentoxifylline renoprotection, pentoxifylline CKD , pentoxifylline nephropathy



## INTRODUCTION

Several new molecules and existing drugs have been evaluated to prolong kidney function in patients suffering from chronic kidney disease.[1] Pentoxifylline(PTX) is one of these agents that is currently indicated for the treatment of intermittent claudication and works to improve blood flow particularly in the limbs.[1] It is designed to reduce the viscosity of blood but also has some effect on inflammatory processes.[2] The anti-inflammatory properties of PTX along with its anti-proteinuric effects have led researchers to investigate its ability to prevent kidney function decline in chronic kidney disease patients. Current pharmacologic therapy for renoprotection includes the use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs). In addition to renin-angiotensin system (RAS) blockade, nonpharmacologic interventions including glycemic, blood pressure control and dietary protein restriction have been proven to slow progression of diabetic and/or non-diabetic chronic kidney disease. However, these therapies do not provide complete kidney protection,[3] and diabetic patients continue to show a high risk, which is positively associated with residual albuminuria.[4] PTX appears to improve circulation by its ability to alter erythrocyte deformability and improve capillary microcirculation and also may act as an adenosine antagonist.[5] This hemorheological property and the potential to decrease intraglomerular pressure led to an early interest in PTX as a therapeutic agent in patients with kidney disease.[6 and 7]

In an animal study conducted in rats, PTX administration enhanced prostacyclin generation by vascular and renal tissue samples.[7] PTX also

**Correspondence Author:** Brian M. Shepler, PharmD, Purdue University College of Pharmacy, 575 Stadium Mall Drive, West Lafayette, Indiana, USA 47907-2091, Tel: 765.494.1365, Fax: 765.494.0801, Email: sheplerb@purdue.edu

appears to have anti-inflammatory properties with demonstrated efficacy in decreasing serum[8] and urinary[9] tumor necrosis factor (TNF) levels in patients with diabetic nephropathy. The magnitude of decrease in proteinuria in patients with diabetic nephropathy was associated with decreased production of the cytokine monocyte chemoattractant protein 1 (MCP-1). A significant correlation existed between the basal urinary protein/Cr and the basal urinary MCP-1/Cr ratios. PTX lowered the urinary MCP-1/Cr ratio, and the percent reduction of urinary protein/Cr ratio correlated directly with the percent decrease of urinary MCP-1/Cr ratio after PTX treatment[10] Animal studies in rats have shown that PTX also decreased renal fibrosis when used in models of pyelonephritis[11] and chronic renal failure,[12] PTX reduced the upregulation of monocyte chemoattractant protein-1 gene by 60%. It also reduced the upregulation of mitogenic and profibrogenic genes by 50%, including platelet-derived growth factor, fibroblast growth factor-2, transforming growth factor-β1, connective tissue growth factor, and types I and III collagen. Furthermore, PTX was found to decrease the numbers of interstitial myofibroblasts by 60% and suppress the proliferation of cultured interstitial fibroblasts. It also reduced the angiotensin II-induced or transforming growth factor-β1-induced expression of connective tissue growth factor gene in cultured fibroblasts and mesangial cells.[12] This mechanism is likely through its ability to inhibit connective tissue growth factor transcription. Furthermore, PTX attenuated tubulointerstitial fibrosis, myofibroblasts accumulation, and expression of CTGF and Col I (α1) in unilateral ureteral obstruction kidneys.[13]

Almost all forms of chronic kidney disease progressing to end-stage renal disease are characterized by diffuse fibrosis, a final common pathway converging from multiple pathogenetic networks regardless of the initial injury. Because of the pathogenetic complexity of kidney disease, multidrug interventions with the least side-effects should, without doubt, be the next step to stop kidney disease progression. Animal and cellular studies have demonstrated the rationale for PTX (i.e. its effects against cell proliferation, inflammation, and extracellular matrix accumulation) in the treatment of chronic kidney disease induced by immune- or non-immune-mediated mechanisms.[14]

Meta-analyses indicate that PTX may reduce proteinuria and that this drug could offer some beneficial effects on kidney function in patients with diabetic kidney disease (DKD).[15] The anti-inflammatory effects conferred by PTX may be beneficial in the management of DKD.[16]
Combining RAS blockade with therapies targeting inflammatory pathways shows the potential to arrest experimental CKD progression.[17, 18 and 20]

This review is intended to evaluate clinical studies in patients already receiving ACE inhibitor or ARB therapy who have received adjunctive PTX therapy to see if additional preservation of kidney function can be achieved.

## METHODS

A search of the literature was conducted using the PubMed.gov and ClinicalTrials.gov search engines and the search terms "pentoxifylline renoprotection", "pentoxifylline CKD", and "pentoxifylline nephropathy". Results were limited to studies in human subjects, published in the English language, and those studies using pentoxifylline as adjunctive therapy to ACEIs and ARBs. No date range was specified. Studies focused on the effects of pentoxifylline on drug induced nephropathy were excluded.

## RESULTS

Using the search methods described above, nine relevant articles were retrieved and evaluated. The two main populations studied were patients with chronic kidney disease (CKD) and patients with CKD and comorbid type 2 diabetes. A summary of these nine studies is provided in Table 1.

In a 2008 study[21] of 85 CKD patients with eGFR of 10-60 mL/min/1.73 $m^2$ and proteinuria >500 mg/g of creatinine, addition of PTX to therapy with 100 mg daily of losartan was shown to lower proteinuria with no statistically significant effect on eGFR. At the time of randomization, patients were divided into 2 groups. During the first stage of the trial which lasted 12 months, group 1 served as the control, while group 2 received PTX therapy. During the second stage which lasted 6 months, both groups received PTX. PTX was dosed at 400 mg twice daily for eGFR 30-60 mL/min/1.73 $m^2$ and once daily for eGFR 10-29 mL/min/1.73 $m^2$. In

**Table 1**. Summary of clinical studies for pentoxifylline as add-on therapy to RAAS inhibition for CKD

| Authors, Year | Study Design | Patients | PTX Dose | Outcomes with PTX Therapy |
|---|---|---|---|---|
| Lin et al. 2008 | RCT | n=85 CKD Patients | eGFR 30-60: 400 mg twice daily<br>eGFR 10-29: 400mg once daily | ↓ Proteinuria, TNF-α, MCP-1<br>↔ eGFR, SCr |
| Perkins et al. 2009 | RCT | n=40 CKD Patients | 400mg twice daily | ↓ Rate of eGFR Decline<br>↔ Proteinuria |
| Renke et al. 2010 | RCT, crossover | n=22 CKD Patients | 1200 mg twice daily | ↔ Proteinuria, NAG, α-1 microglobluin |
| Oliaei et al. 2011 | RCT | n=60 CKD Patients with T2DM | 400 mg three times daily | ↓ Proteinuria<br>↔ eGFR |
| Goicoechea et al. 2012 | RCT | n=91 CKD Patients | 400 mg twice daily | ↓ hs-CRP, TNF-α, serum fibrinogen, ESR<br>↔ eGFR from baseline |
| Ghorbani et al. 2012 | RCT | n=100 CKD Patients +/- T2DM | 400 mg once daily | ↓ Proteinuria<br>↑ CrCl |
| Badri et al. 2013 | RCT | n=18 CKD Patients (Membranous Glomerulonephritis) | 400 mg two or three times daily (depending on CrCl, unspecified) | ↓ Urinary Protein Excretion<br>↔ eGFR |
| Chen et al. 2014 | Retrospective Analysis (subgroups) | n=661 CKD Patients +/- T2DM | 400 mg or 800 mg (depending on eGFR, unspecified) | ↔ Mortality, Proteinuria<br>↓ Risk of ESRD requiring RRT |
| Navarro-Gonzalez et al. 2014 | Open-label, prospective study | n=160 CKD Patients +/- T2DM | 1200 mg daily | ↓ Rate of eGFR Decline, Proteinuria, Urine TNF-α Excretion |

RCT = randomized, placebo-controlled trial
T2DM = type 2 diabetes mellitus
eGFR = estimated Glomerular Filtration Rate
PTX = Pentoxifylline
↓ = statistically significant reduction
↑ = statistically significant increase
↔ = no change

the first stage, the difference between groups was 38.7% (P<0.001), where group 2 showed a 23.9% reduction and group 1 showed a 13.8% increase in proteinura. In the second stage, both groups 1 and 2 showed reductions in overall proteinuria from baseline of 23.8% and 31.3% (P=0.08), respectively. Serum creatinine and eGFR were not significantly different between groups at the end of stages 1 (P=0.1) and 2 (P=0.4), however group 1 showed a statistically significant reduction in eGFR from baseline at the end of stage 1 (p=0.04), while eGFR remained stable in group 2 (p=0.6). PTX was also shown to decrease urinary excretion of TNF-α (P=0.003) and MCP-1(P=0.03) at 12 months, which correlate positively with the change in proteinuria (R=0.64 and R=0.55, respectively; P<0.001 for both), and are believed to be potential causative factors in the progression of CKD.

The following year, a pilot randomized, double-blind, placebo-controlled trial[22] was done to evaluate the effect of PTX on GFR decline in 40 CKD patients with reduced eGFR, hypertension, and proteinuria >1 g/day being treated with either an ACEI, ARB, or combination therapy. Patients were randomized to receive either PTX at 400 mg twice daily or equivalent placebo. After 12 months, it was determined that the mean decrease in GFR in the treatment group was significantly less than that of the control at -1.2 ± 7.0 and -7.2 ± 8.2 mL/min/1.73 $m^2$ (P=0.03), respectively. It was also shown that the mean estimated GFR decrease during treatment was slower than during the year prior to enrollment (P=0.01). This study did not show any significant difference in proteinuria between the treatment and control groups (P-value not reported), indicating the potential independence of proteinuria from the decline of GFR.

Similarly, a randomized, placebo-controlled crossover study[23] of 22 non-diabetic patients taking ACEI's or ARB's was conducted in 2010 which also demonstrated no significant difference in proteinuria. Patients had proteinuria of 0.4-4.3 g/day with normal or reduced kidney function, and blood pressure was controlled at less than 130/80 during an eight week run-in period. Patients were randomly assigned to receive either the PTX, washout, placebo sequence or the placebo, washout, PTX sequence, each of which lasted 8 weeks. PTX was dosed at 1200mg once daily, and doses of ACEI's, ARB's, and diuretics were left unchanged during the study. A reduction in proteinuria in the PTX group versus placebo was observed, however this result was not statistically significant (P=0.11). There were no significant reductions in N-acetyl-β-D-glucosaminidase (P=0.91), or α1-microglobulin (P=0.96) found, and a substantial amount of patients (5 of 24) dropped out of the study due to GI side effects.

The first trial with diabetes patients was a randomized, placebo-controlled trial[24] that enrolled 56 type 2 diabetes patients to examine the effect of PTX on proteinuria and creatinine clearance (CrCl) in 2011. Patients included in the trial had proteinuria >500 mg/day despite treatment with an ACEI or ARB for at least 6 months. The study treatment group received 400 mg PTX three times daily for 3 months. After treatment, reductions of 61.44% and 19.65% were seen in the treatment and placebo groups, respectively, showing a statistically significant reduction (P<0.001). There was no difference in CrCl observed between groups (P=0.08), indicating that the mechanism of reduction of proteinuria by PTX may be independent from mechanisms with the potential to affect CrCl. No major side effects or adverse events were reported.

Ghorbani et al.[25] conducted another randomized controlled trial that looked at the effect of 400 mg daily of PTX on proteinuria and CrCl in 100 patients with type 2 diabetes under angiotensin system blockade in 2012. Patients included in the study had proteinuria >150 mg/day and were treated with both losartan and enalapril for at least 3 months prior to inclusion in the study. Patients were then randomized into two groups with no significant differences at baseline and no significant differences in HbA1C or blood pressure throughout the duration of the trial. PTX was shown to significantly reduce proteinuria from baseline after 6 months by 68.8% in the PTX group (P=0.000) compared to 15.8% in the control group (P-value not reported). In contrast to the 2011 study[24], CrCl was also significantly improved in the PTX group versus the control group (P=0.04).

One randomized, prospective study conducted in 2012[26] considered the effect of 400 mg PTX twice daily on high-sensitivity c-reactive protein (hs-CRP), serum fibrinogen, and TNF-α in 91 patients with CKD. This study also assessed the drug's effect on kidney disease progression as a secondary endpoint by considering eGFR and urine albumin excretion (UAE), and its effects on serum hemoglobin, serum albumin, and erythrocyte sedimentation rate (ESR). At 12 months, significant reductions were observed in the PTX group versus placebo in hs-CRP (p=0.047), serum fibrinogen (p=0.05), TNF- α (p=0.009), and ESR (p=ns). These variables were also statistically significantly reduced from baseline in the PTX group (p=0.02, p=0.001, p<0.001, and p=0.09, respectively). The PTX group also showed stable eGFR, while the control group showed significant worsening of eGFR at 12 months (p<0.001). In both groups, serum hemoglobin and serum albumin remained unchanged.

It is also interesting to note that in a subgroup analysis of diabetic nephropathy patients in the study, albuminuria decreased by 37.2% in the PTX group, while an increase of 72.3% was observed in the control group after 12 months (P-values not

reported). GI symptoms caused 8 patients to withdraw from the study.

The smallest study retrieved was a 6-month randomized, placebo-controlled trial[27] in 18 membranous glomerulonephritis patients. The dose of PTX studied was 400 mg two or three times daily (depending on CrCl), and patients' other RAAS modulating medications were unchanged throughout the duration of the trial. In the group treated with PTX, a statistically significant decrease in urine protein excretion (UPE) as compared to placebo was shown after 6 months of treatment ($p<0.001$), while a minor increase was observed in the control group <p=0.513). eGFR did not change significantly in either group (p=0.807 in the PTX group and p=0.48 in the placebo group) and only 2 patients experienced nausea, which was remedied by taking the drug with meals.

In April 2014, one of the largest studies[28] to date evaluated the use of 400-800 mg PTX (dependent on eGFR) in 661 CKD patients (some with type 2 diabetes)in a retrospective analysis. Patients were divided into high proteinuria (urine protein to creatinine ratio ≥ 1 g/g) and low proteinuria (UPCR < 1 g/g) subgroups, and the study examined progression to renal replacement therapy (RRT) and renal survival analysis as outcomes. The addition of PTX did not have a significant effect on mortality (p=0.74), but did reduce the risk of developing ESRD requiring RRT by 29.5% in the study population (p=0.048). Benefits on renal outcome were more prominent in the high proteinuria subgroup (p=0.005), with no statistically significant effect observed in the low proteinuria subgroup (p=0.33).

Most recently, in June of 2014, the PREDIAN trial[29] was published, examining the effects of 1200 mg daily of PTX (after a one month trial of 600mg daily) on eGFR, UAE, and urine TNF-α. The trial was open label, randomized, and placebo-controlled, and included 82 patients with CKD and comorbid type 2 diabetes. This trial is the longest to date, lasting 2 years. Patients in the PTX therapy group showed statistically significant reductions in the rate of eGFR decline with a difference of 4.3 mL/min/1.73 $m^2$ between groups ($P<0.001$). Patients taking PTX also showed reductions in UAE of 14.9% and 5.7% in the PTX group and the control group, respectively ($P=0.001$). Urine TNF-α excretion was reduced to statistical significance in the PTX group (<0.01), and remained unchanged in the control group. Only 1 patient was unable to complete the study due to the presence of GI side effects; however, 5 patients were unable to tolerate the dose escalation from 600 mg to 1200 mg.

## DISCUSSION AND LIMITATIONS

Our literature review indicated that the examination of the potential antiproteinuric and renoprotective effects of pentoxifylline has recently been an increasingly popular topic in nephrology. It is important to note that all studies included in this review use pentoxifylline as an add on therapy to existing treatment with ACE inhibitors and/or ARBs. Eight of the nine studies we considered analyzed the effect of PTX on proteinuria, while seven of the nine evaluated changes in eGFR and CrCl. Of the eight studies examining proteinuric effects, six showed a significant decrease in proteinuria with PTX use. The two studies that did not show a significant difference were conducted in patients with non-diabetic CKD using different PTX doses. While it is difficult to identify a reason for this discrepancy seen in these results, it is important to note that both studies had a relatively small sample size and may not be indicative of the response of the general CKD population. In addition, the Perkins et al. study did not meet the sample size requirement to effectively power the study. As far as eGFR and CrCl, only four of the seven studies showed significant improvement in these parameters. There appears to be less compelling data indicating that PTX improves or maintains eGFR and CrCl.

The studies evaluated utilized different dosing regimens ranging from 400 mg to 1200 mg daily. Given the half-life of PTX is 0.4 to 1.6 hours, using regimens that include multiple daily dosing would provide the most consistent drug serum concentrations and may be more tolerable to patients. Renke et al. dosed PTX at 1200 mg once daily and experienced the highest amount of patient drop outs due to gastrointestinal side effects. When 1200 mg was given as two 600 mg extended release doses in the PREDIAN trial, only 1 patient dropped out due to GI related side effects. The other trials used a 400 mg dose once or twice daily and had fewer side effects reported. Badri et al. mentions that GI upset was improved when the drug was administered with a meal, which provides another

potential solution for this adverse effect.

PTX does not appear to have any beneficial effect on mortality; however, there was only one study that evaluated this outcome. The PTX treatment group did have a significantly higher number of T2DM patients which may place them at a higher mortality risk and could potentially confound the results. In patients with high proteinuria (i.e., those with urine protein to creatinine ratios ≥ 1 g/g), PTX may reduce the risk of developing ESRD requiring RRT.

## CONCLUSION

For patients with severe proteinuria, PTX may decrease the risk of ESRD requiring RRT. The effect pentoxifylline has on preserving kidney function as determined by eGFR measurements is more difficult to determine as results thus far have been conflicting. More studies are needed to confirm pentoxifylline's ability to maintain or improve eGFR. Based on the side effect profile reported in these trials, 400 mg once or twice daily appears to confer the most benefit with the least amount of GI side effects.

## POST SUBMISSION NOTE

Since the submission of this manuscript, another study evaluated the use of pentoxifylline as adjunctive therapy to ACEI/ARB treatment in those stage 5 CKD patients not yet receiving hemodialysis (CKD 5ND).This nationwide database analysis evaluated over 14,000 patients over a nine year period. The results from this study reported that addition of PTX to existing ACEI/ARB therapy resulted in a decrease risk of long term dialysis or death after propensity score matching in this select group of patients. These findings appear to support the conclusion of this review that PTX may decrease the risk of RRT. This latest study also represents the largest number of patients studied compared to those presented in the above work; however, no specific doses or dose ranges of PTX were included.[30]

## FINANCIAL DISCLOSURE

The authors have no financial interest in this work nor have they received funding of any kind for its production.

## CONFLICTS OF INTEREST

None.

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