A Review of the Potential Benefits of Pentoxifylline in Diabetic and Non-Diabetic Proteinuria

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SUMMARY

Chronic kidney disease (CKD) as a considerable health problem may have proteinuria as the main complication and strong risk factor to reach end-stage renal disease (ESRD). Decreasing proteinuria is the mainstay of therapy in order to delay the progression of CKD. Current therapeutic regimens provide only partial renoprotection, and a substantial number of patients who have proteinuria progress to ESRD. Pentoxifylline (PTF) is known for its potent inhibitory effects against cell proliferation and inflammation which play important roles in CKD progression. Data derived from both human studies and animal models demonstrated that PTF has broad-spectrum renoprotective effects and therefore, provide a scientific basis for the use of PTF as an anti-proteinuric agent.

Conclusion of this review is that short-term use of PTF may produce a significant reduction of proteinuria in subjects with diabetic and also non-diabetic kidney diseases but the reports of long-term use of PTF also show that urinary protein excretion exhibits a progressive and sustained reduction in patients treated with PTF. Whether the long-term use of PTF could be a pharmacological alternative for delaying or preventing the development of end stage renal disease, is among the questions that remained to be appropriately answered in large-scale clinical trials.

INTRODUCTION

Chronic kidney disease (CKD) is a considerable health problem with growing prevalence worldwide as the population ages and the incidence of hypertension and diabetes increases (1). Generally, kidney disease progresses slowly; however, even a small decrease in the rate of kidney function loss results in a marked effect on the time to the development of end-stage renal disease (ESRD) (2). Prevention of renal disease is the most important and effective strategy to decrease the prevalence and incidence of CKD and thus ESRD. Although, a number of diseases that cause CKD are not yet preventable and kidney diseases in most patients are detected at some stages after substantial renal damage (3). The currently available therapeutic interventions for slowing progression of CKD include intensive glycemic control in diabetic patients, strict control of blood pressure, restriction of dietary protein intake, and optimizing renin–angiotensin–aldosterone system (RAAS) blockade.

These interventions actively slow but do not halt the progression of CKD in most cases. In fact, all therapies currently available are only partially effective against the renal end points of ESRD (4, 5).

Proteinuria denotes a sign of glomerular diseases and represents a marker of injury to the glomerular permeability barrier. Proteinuria, even at a sub-nephrotic range, is a well-known risk factor for cardiovascular mortality and morbidity, and strongly associated with the progression of kidney disease. Urinary protein excretion has been used as a surrogate end point for therapeutic interventions of CKD where decreasing proteinuria would delay the progression of CKD, and cardiovascular morbidity (6, 7).

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Although pharmacological inhibition of RAAS has been regarded as the mainstay of therapy for the management of proteinuria, the rate of remission is almost low (8) and side effects are common. Therefore, studies for better drugs are ongoing (9). Because of the pathogenetic complexity of kidney disease, several drugs are usually used together to control kidney disease progression (10-12), but the aim is to achieve the maximal antiproteinuric effect (13).

Pentoxifylline (PTF) is a methylxanthine phosphodiesterase inhibitor which has been in clinical use since the late 1970s and was used primarily to treat patients with peripheral vascular disease (14, 15). In addition to its hemorheologic activity, it has been experimentally shown to have potent antiproliferative, anti-inflammatory (16, 17), anti-diabetic (18), anti cellular damage (19, 20), and antifibrotic effects (21). The hemorheological properties and the potential to improve circulation and some indices of kidney function led to an early interest in the use of PTF as a therapeutic agent in patients with kidney disease (22-24). Data derived from both human studies and animal models provide a strong scientific basis for the use of PTF as an antiproteinuric agent (25-33). The most likely explanation for the antiproteinuric effect of PTF involves its ability to down-regulate the production of proinflammatory cytokines (34, 35). Glomerulonephritis is a proinflammatory state (36), and there is evidence suggesting that proinflammatory cytokines may have a pathogenic role in increasing glomerular permeability to proteins (37). Considering the prognostic impact of proteinuria reduction on long-term renal outcome, and taking into account that PTF exerts favorable hemorheological and anti-inflammatory effects result in reducing proteinuria, the use of PTF in the early stage of proteinuric kidney disease is rationale and seems promising.

In the present review all clinical and non-clinical studies on the use of PTF as an antiproteinuric agent have been evaluated and criticized.

METHODS

Materials for this review were obtained by searching Medline, PubMed, Scopus, Cochrane central register of controlled trials, and Cochrane database systematic reviews. Key words used as search terms were "pentoxifylline", "proteinuria" "urinary protein excretion", "chronic kidney diseases", "kidney disease", and "nephropathy". This search was performed without time limitation. Major well-designed studies which used proteinuria as a main surrogate end point were included.

Non-clinical Studies on the Use of PTF as An Antiproteinuric Agent

Although PTF primarily was indicated for the treatment of peripheral vascular disease,

Table 1. Selected animal studies of antiproteinuric effect of pentoxifylline

Study	Animal models	Administration plan	Study Period	Beneficial effects of PTF
Chen et al (1999) [30]	Rats with anti-Thy1 nephritis	0.1 g/kg/day, IJ infusion	5 days	PTF attenuated proteinuria and glomerular sclerosis
Segal et al (2001) [38]	Rats with immunization-induce SLE-like disease	100 μg daily, IP	6 weeks	PTF decreased proteinuria and immune complex deposition
Lin et al (2002) [16]	Rats with remnant kidney	400 mg/L of drinking water	8 weeks	PTF attenuated proteinuria, interstitial inflammation & renal disease progression
Chen et al (2004) [17]	Rats with crescentic glomerulonephritis	0.1 g/kg/day, IV	28 days	PTF suppressed 24-h urinary protein excretion & progressive renal injury
Usta et al (2004) [29]	Rats with ADR-induced nephropathy	1 g/L of drinking water	21 days	PTF decreased proteinuria, urine nitrite, and apoptosis in the renal tissue
Navarro et al (2006) [39]	Rats with STZ-induced diabetic nephropathy	1 g/L of drinking water	8 weeks	PTF reduced albuminuria & urinary cytokine excretion
Han et al (2010) [31]	Rats with STZ-induced diabetic nephropathy	40 mg/kg, per oral	4 and 8 weeks	Administration of PTF for 4 weeks inhibited the renal inflammatory reaction, & administration for 8 weeks prevented proteinuria

ADR: Adriamycin; IJ: Intra-jugular; IP: Intra-peritoneal; IV: Intravenously; PTF: Pentoxifylline; SLE: Systemic lupus erythematous; STZ: Streptozotocin.

renoprotective and antiproteinuric effects of PTF have been observed in animal studies (Table 1).

In vivo studies have shown beneficial effects of PTF in reduction of proteinuria in different animal models of renal disease, including murine lupus nephritis (38), crescentic glomerulonephritis (17) and an experimental model of adriamycin-induced nephropathy in rats (29). As demonstrated in experimental nephritic rats, one of the possible mechanisms for the renoprotection may be linked to the effect of PTF against the proliferation of glomerular mesangial cells and interstitial fibroblasts (30). A recent work in rats with a remnant kidney demonstrated the significant effects of PTF in modulating inflammation, cell proliferation, and fibrosis. PTF attenuated the progression of renal disease, ameliorated proteinuria, and had a beneficial effect on the renal survival of these rats (16). In addition, in streptozotocin-induced diabetic rats, PTF was effective against the fall in glomerular filtration rate (GFR) and reduced urinary albumin excretion (39).

Recently, the antiproteinuric effect of prolonged administration of PTF was investigated in rats with streptozotocin-induced diabetic nephropathy. The amount of urinary protein was higher in the diabetic rats than that of control group. The amount remained unchanged after 4 weeks and decreased after 8 weeks of PTF treatment. These findings support the hypothesis that prolonged administration enhances the protective effects of PTF (31).

Clinical Use of PTF as an Antiproteinuric Agent in Human Studies
Use of PTF in Diabetic Kidney Disease

The incidence of diabetes is rising, with alarming increases in prevalence of its complications mainly diabetic kidney disease. Diabetic nephropathy is a proinflammatory state, and there is evidence suggesting that proinflammatory cytokines may have a pathogenic role in increasing glomerular permeability to albumin. Currently, treatment of diabetic nephropathy has emphasized on better management of hyperglycemia and control of the RAAS (7, 40). Obviously, current therapeutic regimens have not yet provided satisfactory control of diabetic complications; hence, most of new strategies focused on controlling the GFR decline and proteinuria.

To date, a number of clinical trials evaluating PTF in patients with diabetic kidney disease have been conducted (Table 2). Searching PubMed considering this topic revealed that the first clinical experience of antiproteinuric effect of PTF was reported in 1982 by Blagosklonnaia *et al*. in which some renal function parameters was assessed in 11 diabetic patients who received intravenous PTF 300 mg per day for three weeks. PTF significantly improved GFR and decreased proteinuria in the studied patients (22).

Table 2. Selected clinical studies of antiproteinuric effect of pentoxifylline in diabetic kidney disease

Study	Patient No.	Subjects	Treatment plan	Control Group	Follow up Period	Outcome
Blagosklonnaia *et al* (1982) [19]	11	Diabetic patients with clinical signs of diabetic nephropathy	300 mg daily	-	3 weeks	Marked improvement of renal function: GFR increased, proteinuria diminished
Solerte *et al* (1986) [38]	82	Type 1 and type 2 diabetic patients with microproteinuria	400 mg daily	Without hemorheologic treatment, just more strictly enforced hypoglycemic therapy	Not defined in abstract	Reduction of albumin excretion rate and proteinuria comparable to control group
Solerte *et al* (1987) [39]	21	Type 1 diabetic patients	400 mg daily	Treatment with conventional antihypertensive therapy	1 year	Reduction of urinary albumin/total protein excretion rate comparable to comparable to control group

Guerrero-Romero et al (1995) [23]	86	Type 1 and type 2 diabetes with a wide range of urinary protein excretion	1200 mg daily	Placebo	4 months	Overt proteinuria and microalbuminuria significantly decreased compared to placebo group
Navarro et al (1999) [40]	24	Diabetic patients with advanced renal failure	400 mg daily	Untreated control group	6 months	Proteinuria significantly decreased in PTF group compared to control group
Navarro et al (2003) [41]	45	Patients with early type 2 diabetic nephropathy	1200 mg daily	Untreated control group	4 months	PTF combined with RAAS blockade further reduced proteinuria and protect the kidney compared to control group
Navarro et al (2005) [13]	61	Normotensive patients with diabetic nephropathy and residual albuminuria	1200 mg daily + recommended doses of ARB	Treatment with recommended doses of ARB	4 months	Significant additive antiproteinuric effect compared to control group
Harmankaya et al (2003) [42]	50	Type 2 diabetic patients	600 mg daily + lisinopril 10 mg daily	Lisinopril 10 mg daily	9 months	Significant additive antiproteinuric effect compared to control group
Aminorroaya et al (2005) [43]	39	Type 2 diabetic patients	1200 mg daily	Captopril 75 mg daily	2 months	PTF was as effective as captopril in reducing overt proteinuria
Rodriguez-Moran et al (2005) [44]	130	Type 2 diabetic patients	1200 mg daily	Captopril 75 mg daily	6 months	PTF was as effective as captopril in reducing microalbuminuria
Rodriguez-Moran et al (2006) [45]	40	Type 2 diabetes and microalbuminuria	1200 mg daily	Placebo	16 weeks	Microalbuminuria significantly decreased compared to placebo group
Diskin et al (2007) [46]	7	Diabetic men with primarily nephrotic-range proteinuria	PTF dose adjusted for creatinine clearance + Maximal doses of ACEIs and ARBs	Treatment with maximal doses of ACEIs and ARBs	1 year	Non-significant trend toward improvement in proteinuria compared with control group
Roozbeh et al (2010) [47]	74	Type 2 diabetic patients with overt proteinuria	1200 mg daily + captopril 75 mg daily	Captopril 75 mg daily	6 months	Proteinuria reduction in PTF group was nearly three-fold that of control group

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; GFR: Glomerular filtration rate; PTF: Pentoxifylline; RAAS: Renin–angiotensin–aldosterone system.

In the past few years there has been ongoing interest in the use of PTF as an antiproteinuric agent in patients with a variety of renal diseases, mostly diabetic nephropathy. The early randomized controlled clinical trials demonstrating the beneficial effect of oral PTF in the reduction of microproteinuria were first published in 1986 and further investigated in 1987 by Solerte and

colleagues. According to the results of these two studies, a significant improvement of blood rheology pattern together with a marked reduction of urinary albumin and total protein excretion rates were demonstrated in the diabetic patients treated with PTF (41, 42). These studies indicate that PTF may be effective for preventing or delaying the progression of kidney disease and might be useful in the treatment of diabetic microproteinuria.

In one randomized double-blind placebo-controlled study published in 1995, Guerrero-Romero *et al.* assessed the effect of PTF in 86 patients with type 1 and type 2 diabetes with a wide range of urinary protein excretion. Patients randomly allocated to receive either PTF 1200 mg daily or placebo for four months. Both overt proteinuria and microalbuminuria significantly decreased in the patients with both types of diabetes who received PTF compared with control subgroups who received placebo (26). These results confirmed previous findings reporting an antiproteinuric effect of PTF in patients with diabetic nephropathy.

Limited short-term human studies proved PTF add-on efficacy in decreasing proteinuria in patients with diabetes using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). In a clinical trial by Navarro *et al.* in 1999, 24 diabetic patients with advanced renal failure were randomly allocated to receive PTF (400 mg daily) for 6 months or no additional treatment. Monotherapy with PTF markedly decreased proteinuria of diabetic patients. Conversely, proteinuria was not changed in the control group. None of the studied patients received ACEI or ARB (43). Soon after in 2003, Navarro *et al.* evaluated the additive antiproteinuric effect of PTF in 30 patients with early type 2 diabetic nephropathy who were already receiving treatment with ACEI or ARB. Administration of PTF (1200 mg daily) for 4 months in these patients further reduced urinary protein excretion compared with data from a control group (44). These findings suggest that PTF may have beneficial effects on tubulointerstitial damage in patients with diabetic kidney disease and provide clinical evidence that PTF combined with RAAS blockade may further reduce proteinuria and protect the kidney.

Navarro *et al.* further investigated this hypothesis by conducting another study in 2005 in order to assess the additive antiproteinuric effect of oral PTF in type 2 diabetic patients. In this study, 61 patients with diabetic nephropathy and residual albuminuria despite treatment with the appropriate doses of ARB for more than one year, were randomly assigned to receive the addition of 1200 mg of PTF daily or to a control group (13). This hypothesis was also tested in 2003 by Harmankaya *et al.* in which the combination of PTF (600 mg daily for 9 months) with ACEI was assessed regarding additional reduction in microalbuminuria in 25 type 2 diabetic patients compared to a placebo group (45). In both of these randomized placebo-controlled studies, the authors concluded that administration of PTF to diabetic patients under long-term treatment with an ACEI or ARB produces a significant additive antiproteinuric effect.

Two other studies published in the same year compared the antiproteinuric effect of PTF with an ACEI, captopril, in type 2 diabetic patients which randomly allocated to receive oral PTF (1200 mg daily) or captopril (25 mg three times per day) for two (46) or six (47) months. PTF has been demonstrated to be as effective as captopril in reducing overt proteinuria and microalbuminuria in type 2 diabetic patients, suggesting that PTF could be an effective alternative to ACE inhibitors in reducing urinary protein excretion.

Recently, in order to identify the effect of PTF on the urinary protein excretion in patients not treated with RAAS inhibition, a clinical trial was conducted among 40 patients with type 2 diabetes and microalbuminuria. At the end of follow-up, microalbuminuria significantly decreased in the patients who received PTF (1200 mg daily, for 16 weeks), and remained without significant changes in the subjects with placebo. Also, it is demonstrated that PTF significantly reduces the urinary excretion of both low and high molecular-weight proteins (48).

Diskin *et al*, in a small nonrandomized trial examined the impact of PTF on kidney function in patients with advanced CKD currently using RAAS inhibition. This study included 7 diabetic men with primarily nephrotic-range proteinuria and advanced CKD on maximal doses of both an ACE inhibitor and an ARB, and showed that PTF therapy for 1 year produced a non-significant trend toward improvement in proteinuria compared with matched controls. Although no significant difference in rate of decrease in kidney function was identified, the

PTF group had nearly 50% less decrease during the one year-long study compared with the control group (49).

Most recently, antiproteinuric efficacy of combining an ACE inhibitor, captopril, and PTF was evaluated in 74 type 2 diabetic patients with overt proteinuria. Patients randomly assigned to two groups (group 1: captopril 25 mg three times a day, group 2: captopril 25 mg and PTF 400 mg each three times per day). The reduction in urinary protein excretion was similar in the two groups until the end of the second month, while at six months, the reduction in group 2 (PTF + captopril) was nearly three-fold that of group 1 (captopril). Authors concluded that combining an angiotensin-converting enzyme inhibitor and PTF can lead to a greater reduction in proteinuria (50).

The clinical evidences that show the efficacy of PTF in the management of microalbuminuria in diabetic patients were reviewed by Rodriguez-Morán, *et al*. According to this review, current evidence consistently shows that short-term use of PTF significantly reduces both the overt proteinuria and microalbuminuria in subjects with diabetes suggesting that PTF could be useful for the treatment of diabetic nephropathy (9).

These positive effects were summarized by McCormick and colleagues in a meta-analysis reviewing all randomized controlled trials that involved adult patients with proteinuria secondary to diabetic kidney disease who received oral PTF (7). Based on statistical analysis, the authors concluded that PTF is an efficacious antiproteinuric agent (versus placebo or usual care) with a significant impact only in overt proteinuria (urine protein > 300 mg/d), but no significant change in microalbuminuria. Although, the main limitations of their review are that the studies included small numbers of patients, were of short duration, used different doses of PTF and that methods quality was poor.

Use of PTF in Non-Diabetic Kidney Disease

Parallel to the findings on diabetic nephropathy, clinical trials in patients with non-diabetic renal diseases such as membranous glomerulonephritis

Table 3. Selected clinical studies of antiproteinuric effect of pentoxifylline in non-diabetic kidney disease

Study	Patient No.	Subjects	Treatment plan	Control Group	Follow up Period	Outcome
Ducloux *et al* (2001) [48]	10	Biopsy-proved membranous nephropathy	1200 mg daily	-	6 months	Remission of proteinuria
Chen *et al* (2006) [32]	17	Non-diabetic patients with primary glomerular disease and persistent proteinuria	800 mg daily	-	6 months	Urinary protein excretion reduced significantly
Galindo-Rodriguez *et al* (2003) [49]	11	Refractory nephrotic syndrome and proteinuria despite immunosuppressive therapy	800-1600 mg daily	-	6 months	Proteinuria reduced significantly
Renke *et al* (2010) [50]	22	Non-diabetic patients with proteinuria	1200 mg daily + ACEI or ARB	Placebo + ACEI or ARB	8 weeks	Proteinuria reduced
Lin *et al* (2008) [51]	85	Patients with CKD and proteinuria	400-800 mg daily	Untreated control group	12 months	Proteinuria decreased, No notable change in GFR
Perkins *et al* (2009) [52]	40	Patients with CKD	800 mg daily	Placebo	1 year	Slower decrease in GFR, Proteinuria was not different between group

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CKD: Chronic kidney disease; GFR: Glomerular filtration rate.

and lupus nephritis have also shown that PTF can attenuate proteinuria in these types of kidney diseases. Clinical trials demonstrating antiproteinuric effect of PTF in patients with non-diabetic renal diseases are summarized in Table 3.

In a prospective pilot study on 10 patients with biopsy-proved membranous nephropathy and persistent nephrotic syndrome despite maximum ACEI treatment, Ducloux *et al*. demonstrated that in nine patients received PTF treatment (1200 mg/day) for 6 months, remission of proteinuria was achieved. Importantly, these patients did not receive any immunosuppressive therapy (51). The antiproteinuric effect of PTF (400 mg twice daily, for 6 months) was also demonstrated in a small study in 17 non-diabetic patients with primary glomerular disease (34). Also, Galindo-Rodriguez *et al*. demonstrated that add-on PTF (800-1600 mg/day) for 6 months significantly reduced proteinuria in 11 patients with refractory nephrotic syndrome and proteinuria despite immunosuppressive therapy (52).

In a placebo-controlled, randomized study, the influence of PTF (1200 mg/day) added to RAAS blockade on proteinuria, was evaluated in 22 non-diabetic patients with proteinuria in an eight-week run-in period. PTF therapy reduced proteinuria (by 26%) in this population as compared to placebo (53).

A randomized controlled study evaluated the additional effect of PTF on proteinuria and GFR in 85 patients with CKD who were already receiving the ARB, losartan. PTF added to losartan therapy for 1 year decreased proteinuria in patients with CKD stages 3 to 5, but no notable change was seen in GFR (54). In contrast, different results have been seen in a placebo-controlled study by Perkins *et al*, in which the efficacy of PTF (400 mg twice daily) to slow the GFR decrease and attenuate proteinuria was evaluated in 40 patients with chronic kidney disease. According to the results, for PTF-treated participants, the mean estimated GFR decrease during treatment was slower compared with the year before study enrollment, but proteinuria was not different between the PTF and placebo groups at baseline, 6 months, or 1 year. The authors concluded that PTF may slow the estimated GFR decrease in high-risk patients and this may be independent of its antiproteinuric properties (55).

CONCLUSION

In summary, a total of 7 animal studies, 13 randomized controlled trials on diabetic kidney disease, and 6 studies on a variety of non-diabetic kidney diseases have been reviewed. The results from most of these studies consistently demonstrate that short-term use of PTF produce a significant reduction of proteinuria and microalbuminuria in patients with diabetic and also non-diabetic kidney diseases (13, 26, 44, 46, 48, 53). The reports of long-term studies (42, 43, 45, 47, 49-52) also show that urinary protein excretion exhibits a considerable reduction in patients treated with PTF; however, since these results are mostly based on clinical trials of small size, whether the additive antiproteinuric effect of PTF is sustained over time, and whether the long-term use of PTF could be a pharmacological alternative for delaying or preventing the development of ESRD, are among the questions that remained to be appropriately answered in large-scale clinical trials.

Also, data on the antiproteinuric effect of PTF in a wide range of non-diabetic kidney diseases are scarce. Only a few randomized controlled trials directly addressing the effect of PTF on renal function and proteinuria in non-diabetic patients have been reported. Most of those studies were of small size or short duration, and many did not include a placebo arm. Membranous nephropathy (MN) was the subject of one of these studies. Despite a multitude of investigation over the last years, the treatment of membranous nephropathy remains both controversial and suboptimal. Recent progress in the molecular pathways of inflammation and immunologic regulation warrants further investigation on probable alternatives to the standard regimen of glucocorticoids and alkylating agents (56). Among the studied alternatives, PTF has shown its ability to reduce proteinuria in the solely study in patients with MN. In this pilot study described previously (51), monotherapy with PTF markedly reduced proteinuria in 10 patients with MN who were not receiving any other medication. This study did not include the placebo arm. Indeed, the PTF's benefit when administered in conjunction with standard treatment protocol in patients with most non-diabetic kidney diseases is not clear. Considering the prognostic impact of proteinuria reduction on long-term renal outcome in progressive kidney diseases namely MN, we

designed a six-months randomized placebo-controlled study evaluating the antiproteinuric effect of PTF addition to background nephroprotective therapy consisting of ACEI and/or ARB, glucocorticoids and alkylating agents in patients in which MN was newly diagnosed based on histological studies. The study is now recruiting and the results will be released in 2014. This study may help to answer the question of whether PTF further improves renal outcome in MN patients already receiving standard therapy.

Future Perspective

Proteinuria is a well-recognized risk factor for cardiovascular and renal disease; hence, its early pharmacological treatment is a matter of clinical relevance. Little treatment is available to promote the reduction of proteinuria once that is established. In this regard, although ACE inhibitors have been cited as the first line of therapy, new data showing the beneficial effect of PTF on the reduction of microalbuminuria and overt proteinuria are rapidly increasing. Major studies focused on the use of PTF as an antiproteinuric agent reviewed here. Almost all studies showed that PTF administration to patients with proteinuric nephropathy was associated with a significant reduction of proteinuria after short- or long-term follow-up. However, the findings of presently described studies need to be confirmed in adequately powered, high-quality controlled trials before recommending the use of PTF in patients with progressive CKD. During the next years, the results of ongoing trials will ultimately determine whether PTF can really benefit clinical outcomes of this devastating disease.

ACKNOWLEDGMENT

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