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Uric acid lowering for slowing CKD progression after the CKD-FIX trial: a solved question or still a dilemma?

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ABSTRACT

Hyperuricemia has been associated with several cardiovascular risk factors and is a well-known predictor of kidney disease. *In vitro* studies as well as animal models highlighted a role for uric acid in the development and progression of haemodynamic and tissue damage at the renal level leading to glomerular and tubulointerstitial abnormalities. Urate-lowering treatment, especially by xanthine oxidase inhibitors, has been proposed in order to improve kidney outcomes. However, recent randomized controlled trials failed to demonstrate a beneficial effect of allopurinol or febuxostat on renal disease, casting doubts on the role of this therapeutical approach to improve nephroprotection. We provide a critical overview of current literature on this topic and offer a possible interpretation of results from recent intervention trials with urate-lowering treatment on renal outcomes.

Keywords: allopurinol, chronic kidney disease, disease progression, hyperuricemia, nephroprotection, urate-lowering treatment, uric acid

INTRODUCTION

Chronic kidney disease (CKD) is a public health problem of growing dimensions worldwide. This is due to the rising prevalence of diabetes mellitus, hypertension and obesity, as well as population aging [1], the main risk factors for chronic renal damage. Regardless of its aetiology, the development of CKD is associated with a dramatic increase of cardiovascular morbidity and mortality as well as with faster progression to end-stage kidney disease (ESKD) and the need for renal replacement therapy. Current therapeutic strategies to slow down glomerular filtration rate (GFR) deterioration have traditionally been based on reduction of blood pressure and albuminuria (if present) preferably with the use of renin–angiotensin–aldosterone system (RAAS) inhibiting drugs and, more recently, with the use of sodium–glucose cotransporter-2 inhibitors (SGLT2is). This approach, however, has provided only limited results so far and most CKD patients witness a progressive loss of renal function over time. There is a huge unmet need to validate and implement novel and effective therapeutic strategies.

Hyperuricemia, even when asymptomatic, is a relatively common disorder and it has been associated with several conditions that are known to increase cardiovascular risk, such as hypertension, metabolic syndrome and type 2 diabetes (Figure 1). Furthermore, there is a convincing clinical and experimental evidence linking hyperuricemia to CKD, including albuminuria [2, 3], GFR reduction [4, 5] and progression to ESKD [6], although several confounding variables may limit the interpretation of

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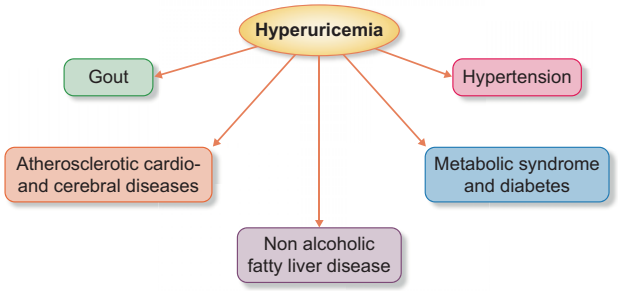

FIGURE 1: Extrarenal clinical correlates of hyperuricemia.

results and some studies failed to confirm this association [7, 8]. From a pathophysiological standpoint, the dual relationship between increasing serum uric acid values and GFR reduction makes for a complex scenario, wherein hyperuricemia may be both a promoter and simply a result of kidney damage. Although longitudinal data support a role for increased uric acid as an independent predictor of future renal function decline, uric acid levels are known to be affected by several factors that might have greatly influenced the results of observational studies [9]. Only interventional studies demonstrating a beneficial effect of urate-lowering treatment (ULT) may finally resolve the issue and provide serum uric acid the status of a real renal risk factor.

However, the nephroprotective effect of treating hyperuricemia has been debated in the last years. In fact, until recently, available literature on this issue was limited to small size, often non-randomized single-centre trials, with a limited follow-up time [10–21] (Table 1). Thus, the KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease published in 2012 concluded that there was 'insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD' [22].

Later on, a systematic review and random-effects meta-analysis which included eight randomized controlled trials (RCTs) with a total of 476 participants evaluating allopurinol treatment on renal outcomes suggested that xanthine oxidase (XO) inhibitor allopurinol might retard the progression of CKD, despite a substantial heterogeneity in baseline renal function, aetiology of CKD and duration of follow-up across studies [23]. The authors concluded that adequately powered randomized trials were strongly needed to evaluate the benefits and risks of ULT in CKD.

Over the last years, some randomized, double-blind, placebo-controlled trials have been designed specifically to test the hypothesis that ULT would slow CKD progression in order to resolve the uncertainty on the role of uric acid-lowering in terms of nephroprotection.

The present manuscript aims at providing a critical overview of current literature on this topic and a possible explanation for the lack of nephroprotective effect of ULT on CKD progression, indicating remaining unmet needs and future research directions.

RENAL EFFECTS OF HYPERURICEMIA

Uric acid levels are affected by several factors. In humans, the loss of uricase, the major uric acid catabolic enzyme, in the course of evolution has made uric acid-circulating levels exclusively dependent on the net balance of its production and excretion. The production of uric acid largely results from purine catabolism and is greater in patients with a high intake of dietary proteins, alcohol and fructose, while the excretion largely depends on kidney function. Furthermore, insulin resistance, the use of diuretics and hypovolemia increase kidney reabsorption of uric acid and are, therefore, associated with higher uric acid levels [24]. The mechanisms by which uric acid induces renal damage seem to go beyond the deposition of crystals at the tubular level [25], and likely involve several pathophysiologic mechanisms such as oxidative stress, arteriosclerosis and glomerular hypertension [26–29] (Figure 2). At present, two pathways for hyperuricemia-induced renal damage have been clarified at the tissue level. First, the recognition of uric acid as a dangerous substance by receptors involved in the innate immune response is likely to trigger an inflammatory cascade that leads to renal fibrosis [30–33]. Second, serum uric acid may elicit renin–angiotensin system activation and nitric oxide synthesis inhibition, favoring endothelial dysfunction and proliferation of vascular smooth muscle cells, leading to glomerulosclerosis and interstitial fibrosis [34, 35]. Interestingly, *in vivo* studies have demonstrated that treatment with XO inhibitors, such as allopurinol or febuxostat, is able to decrease tubulointerstitial fibrosis in 5/6 nephrectomy model and in diabetic nephropathy [36, 37]. Furthermore, a recently published basic research study in a mouse model indicates that uric acid by crystallizing in acidic tubular fluid may cause tubular injury, inflammation, and interstitial nephritis and fibrosis, and subsequently granulomatous interstitial nephritis contributing to CKD progression [38].

RCTS AND RENAL PROTECTION

Very recently, two large, long-awaited RCTs on the effect of allopurinol on the progression of CKD were completed and published [39, 40]. Briefly, both studies were multicentric and conducted on patients at high renal risk with either albuminuria or evidence of rapid decline in estimated GFR (eGFR).

In the Preventing Early Renal Loss in Diabetes (PERL) Trial, allopurinol was tested against placebo in 530 patients with type 1 diabetes and evidence of kidney disease, i.e., mild-to-moderate increase in albuminuria and eGFR between 45 and 100 mL/min × 1.73 m^2 (with a mean level of approximately 70 mL/min × 1.73 m^2) or significant GFR loss, i.e., >3 mL/min × 1.73 m^2/year, in the previous 3–5 years.

The Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase (CKD-FIX) included 363 diabetic and non-diabetic patients with stage 3 or 4 CKD (mean eGFR approximately 30 mL/min × 1.73 m^2) and albumin to creatinine ratio (ACR) ≥265 mg/g or eGFR decline rate ≥3.0 mL/min × 1.73 m^2 in the preceding 12 months.

In both studies, the decline of eGFR was significant during the follow-up (approximately −2.5 mL/min × 1.73 m^2 per year in PERL and 3.3 mL/min × 1.73 m^2 per year in CKD-FIX) indicating that both study cohorts were at high risk of progression to ESKD, a setting in which the potential renal benefit of treatment might be relevant and easy to demonstrate. Furthermore, in both studies, an effective and sustained reduction in uric acid was obtained in the active treatment arm as compared with placebo. In the PERL study, mean uric acid decreased in the allopurinol group from 6.1 at baseline to 3.9 mg/dL during treatment, whereas it remained at 6.1 mg/dL in the placebo group. Similarly, in the CKD-FIX trial, mean uric acid levels remained constant in the placebo group and decreased in the allopurinol group to 5.1 mg/dL at 12 weeks and remained at 5.3 mg/dL along the study period with an approximately 35% reduction substantially superimposable to that observed in the PERL study (36%). However, both studies showed negative

Table 1. RCTs on the effectiveness of urate-lowering treatment on renal function in patients with chronic kidney disease

Study	Study design	Study drug	Population	Duration (months)	Change in renal function in T group	Change eGFR in C group	P	Other renal outcomes
Siu *et al.* 2006 [10]	Parallel, placebo RCT	Allopurinol ($n = 25$) *versus* usual therapy ($n = 26$)	Hyperuricemic patients with CKD defined as proteinuria >0.5 g and/or an sCr >1.35 mg/dL)	12	sCr +1.03 mg/dL	sCr +0.35 mg/dL	0.08	Combined endpoint of significant deterioration in renal function and dialysis: 16% in T and 46.1% in C ($P = 0.015$)
Malaguarnera *et al.* 2009 [11]	Parallel, placebo RCT	Rasburicase ($n = 20$) *versus* placebo (n =1 8)	Hyperuricemic elderly patient	2	ClCr +12.7 mL/min	ClCr −0.9 mL/min	<0.001	
Goicoechea *et al.* 2010 [12]	Parallel RCT	Allopurinol ($n = 57$) *versus* usual therapy ($n = 56$)	CKD (eGFR <60 mL/min × 1.73 m^2)	24	eGFR +1.3 mL/min × 1.73 m^2	eGFR −3.3 mL/min × 1.73 m^2	0.018	
Momeni *et al.* 2010 [13]	Parallel, placebo RCT	Allopurinol ($n = 20$) *versus* placebo ($n = 20$)	Diabetic patients with nephropathy (proteinuria >500 mg/d and sCr <3 mg/dL)	4	sCr +0.00 mg/dL	sCr +0.3 mg/dL	0.180	
Shi *et al.*, 2012 [14]	Parallel, RCT	Allopurinol (n=21) *versus* usual therapy ($n = 19$)	Hyperuricemic IgAN patient, non-nephrotic, sCr <3 mg/dL	6	eGFR +3.7 mL/min × 1.73 m^2	eGFR +5.3 mL/min × 1.73 m^2	0.200	
Goicoechea *et al.* 2015 [15]	Post-hoc follow-up RCT	Allopurinol ($n = 56$) *versus* usual therapy ($n = 51$)	CKD (eGFR <60 mL/min × 1.73 m^2)	84	eGFR −6.5 mL/min × 1.73 m^2	eGFR −13.3 mL/min × 1.73 m^2	0.001	Renal event (defined as starting dialysis therapy and/or doubling serum creatinine and/or ≥50% decrease in eGFR) [hazard ratio 0.32 (95% confidence interval 0.15–0.69) $P = 0.004$}
Tani *et al.* 2015 [16]	Prospective, Open-label study	Febuxostat ($n = 30$) *versus* no treatment ($n = 30$)	Hyperurecemic patients with hypertension	6	eGFR +3.7 mL/min × 1.73 m^2	eGFR −3.4 mL/min × 1.73 m^2	0.006	
Sircar *et al.* 2015 [17]	Parallel, placebo RCT	Febuxostat ($n = 45$) *versus* no treatment ($n = 48$)	Adults 18–65 years with CKD stages 3 and 4, with asymptomatic hyperuricemia	6	eGFR + 3.2 mL/min × 1.73 m^2	eGFR −4.4 mL/min × 1.73 m^2	0.05	>10% decline in eGFR: 38% in T and 54% in C ($P < 0.004$)
Tanaka *et al.* 2015 [18]	Parallel, open-label RCT	Febuxostat ($n = 21$) *versus* usual therapy ($n = 19$)	Hyperuricemic patients with CKD stage 3	3	eGFR −1.3 mL/min × 1.73 m^2	eGFR −0.4 mL/min × 1.73 m^2	NS	
Saag *et al.* 2016 [19]	Parallel, placebo RCT	Febuxostat 30 mg BID ($n = 17$) *versus* Febuxostat (40–80 mg/d ($n = 25$) *versus* placebo ($n = 15$)	Hyperuricemic patients with gout and moderate-to-severe renal impairment (eGFR 15–50 mL/min × 1.73 m^2), gout and hypertension	12	sCr +0.09 mg/dL (T 30 mg BID)	sCr +0.19 mg/dL	0.459	

Table 1. Continued

Study	Study design	Study drug	Population	Duration (months)	Change in renal function in T group	Change eGFR in C group	P	Other renal outcomes
					+0.23 mg/dL (T 40–80 mg/d)	+0.19 mg/dL	0.789	
					eGFR +0.33 mL/min × 1.73 m^2 (T 30 mg BID)	eGFR −2.05 mL/min × 1.73 m^2	0.162	
					−0.86 mL/min × 1.73 m^2 (T 40–80 mg/d)	−2.05 mL/min × 1.73 m^2	0.485	
Beddhu *et al.* 2016 [20]	Parallel, placebo RCT	Febuxostat ($n = 39$) *versus* placebo ($n = 37$)	Overweight or obese adults with hyperuricemia and DKD (eGFR 30–60 mL/min × 1.73 m^2)	6	eGFR −3 mL/min × 1.73 m^2	eGFR −3 mL/min × 1.73 m^2	NS	
Mukri *et al.* 2018 [21]	Parallel, open-label RCT	Febuxostat ($n = 47$) versus no treatment ($n = 46$)	CKD stage 3 and 4 patients	6	eGFR +0.3 mL/min × 1.73 m^2	eGFR −0.6 mL/min × 1.73 m^2	<.01	

CKD, chronic kidney disease; ClCr, creatinine clearance; d, day; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy; NS, not significant; sCr, serum creatinine.

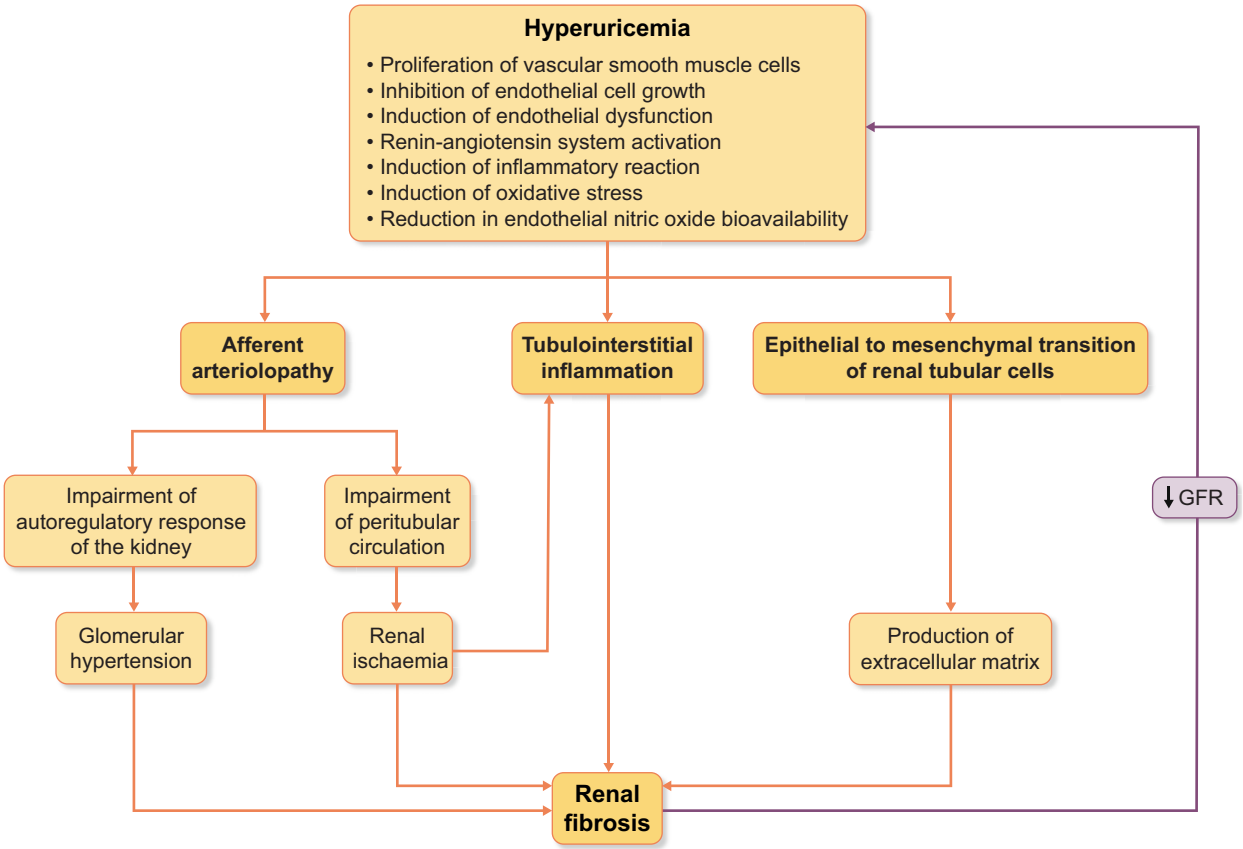

FIGURE 2: Potential mechanisms of uric acid-mediated renal adverse effects.

results in terms of nephroprotection, since the decline of GFR was similar between the two groups during the follow-up.

These results were consistent with those of the FEATHER study (Febuxostat versus Placebo Randomized Controlled Trial Regarding Reduced Kidney Function in Patients with Hyperuricemia Complicated by Chronic Kidney Disease Stage 3) [41], a previously published RCT on the same topic with the use of febuxostat. Main details and principal results of these three trials are reported in Table 2.

A recent published meta-analysis with 3934 participants on the effect of ULT on cardiovascular and renal outcomes that included all these three RCTs showed that active treatment with XO inhibitors does not produce benefit on clinical outcomes, including major adverse cardiovascular events, all-cause mortality and kidney failure (defined as at least 30% decrease in eGFR, doubling of serum creatinine or kidney failure as defined in each study) [42]. Actually, the analysis suggested that ULT might have a potential to slow the decline of GFR, but the effect was driven mainly by trials with short follow-up or low quality. As a matter of fact, the trials included in this meta-analysis do show significant heterogeneity related to the level of baseline renal function, underlying disease and other conditions such as the use of RAAS inhibitors or significant discontinuation rate that could have affected the results.

ULT AND KIDNEY OUTCOME: WHERE ARE WE NOW?

On the whole, these results do not seem to support a beneficial role for uric acid reduction in the course of CKD and, therefore, do not justify the use of XO inhibitors in order to slow down GFR deterioration. However, this important clinical issue seems far from being definitively settled and the last word may not have been said yet [43, 44]. In fact, these trials recruited a relatively small number of patients and the observed lack of benefit with XO inhibitors, which may have been due to several other reasons. While no specific cut-off uric acid value was implemented as inclusion criteria in the CKD-FIX study, the mean baseline uric acid level was considerably elevated, i.e., 8.2 mg/dL, the highest value among the three trials. Furthermore, the severity of renal disease (only patients with stage 3–4 CKD were included) could have limited the ability of allopurinol to prevent further decline in the GFR. In fact, once renal lesions become established, the protective effect of urate-lowering treatment may weaken similar to what has been reported for hypertension [45]. Furthermore, in the PERL study, patients had a very long duration of type 1 diabetes (34.6 years) which may have had exerted an unfavourable and irreversible impact on renal outcome. Despite mild or no clinical renal damage at baseline they turned out to be fast progressors as indicated by their slope of eGFR reduction (about 2.5–3 mL/min × 1.73 m^2/year). In this regard, results of the FEATHER study [41] may leave room to hypothesize a protective renal effect of ULT. For once, febuxostat, which is known to be a more specific and powerful ULT agent as compared with allopurinol, might prove to be more effective in patients with very early stages of kidney damage such as those without proteinuria and those with a serum creatinine below the median. Accordingly, in the FREED study (Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy), a larger randomized study with a follow-up

Table 2. Major clinical trials on renal outcome with XO inhibitors at comparison

	FEATHER [41]	PERL [39]	CKD-FIX [40]
Study design	Prospective, double-blind, randomized, placebo-controlled, superiority trial	Prospective, double-blind, randomized, placebo-controlled, superiority trial	Prospective, double-blind, randomized, placebo-controlled, superiority trial
Site	Multicentre in Japan (64 sites total)	Multicentre in USA, Canada and Denmark (16 sites total)	Multicentre in Australia and New Zealand (31 sites total)
Study drug	Febuxostat *versus* placebo	Allopurinol *versus* placebo	Allopurinol *versus* placebo
Study design	Febuxostat dose: - Weeks 1–4: 10 mg/d - Weeks 5–8: 20 mg/d - Weeks 8–108: 40 mg/d	- RAS inhibitors run-in period (2 months) - Randomization - Treatment period (3 years) - Wash-out period (2 months) Allopurinol dose: - 400 mg/d if eGFR ≥50 mL/min × 1.73 m^2 - 300 mg/d if eGFR 25–49 mL/min × 1.73 m^2 - 200 mg/d if eGFR <25 mL/min × 1.73 m^2	- Randomization - Dose escalation period (12 weeks) - Treatment period (92 weeks) Allopurinol dose: 400 mg/d or 100–300 mg/d according to pre-specified safety criteria
Population	≥20 yrs or older with: - Hyperuricemia (SUA 7.1–10 mg/dL) without gouty arthritis - CKD stage 3	Adults with T1DM and: - eGFR 40–99.9 mL/min/1.73 m^2 - DKD - UAER 20–3333 ug/min or UACR 30–5000 mg/g if not on RASi or UAER 12–3333 ug/min or UACR 18–5000 mg/g if on RASi or not specified level if historical eGFR decline ≥3 mL/min × 1.73 m^2/year - SUA ≥4.5 mg/dL	Adults with: - CKD stage 3 or 4 - UACR ≥265 mg/g or not specified minimum level if historical eGFR decline ≥3 mL/min × 1.73 m^2/year
Baseline characteristics	- 77% men - Mean age: 65 years - 31% DM - Mean eGFR: 44.9 mL/min × 1.73 m^2 - UACR 717 mg/g - Mean SUA: 7.8 mg/dL - 73% on RASi before the study	- 66% men - Mean age: 51 years - Mean T1DM duration: 34.6 years - Mean HbA1c: 8.2% - Mean iGFR: 68 mL/min × 1.73 m^2 - Mean eGFR:74.7 mL/min × 1.73 m^2 - Mean SUA: 6.1 mg/dL - 90% on RASi before the study	- 63% men - Mean age: 63 years - 58% DM - Mean eGFR: 31.7 mL/min × 1.73 m^2 - Median UACR 717 mg/g - Mean SUA: 8.2 mg/dL - 76% on RASi before the study
Primary outcome results	eGFR slope Results: difference NS Febuxostat (0.23 ± 5.26 mL/min × 1.73 m^2 per year) and placebo (−0.47 ± 4.48 mL/min × 1.73 m^2 per year) groups [difference, 0.70 mL/min × 1.73 m^2 (95% CI −0.21 to 1.62); P = 0.1]	Change in iGFR Results: difference NS (difference between group 0.001 mL/min × 1.73 m^2 per year)	Change in eGFR Results: difference NS (difference between group 0.1 mL/min × 1.73 m^2 per year)
Secondary outcome results	Subgroup analysis of the eGFR slope showed a significant difference of 1.79 mL/min × 1.73 m^2 per year (P = 0.005) in patients without proteinuria and a significant difference of 1.76 mL/min × 1.73 m^2 per year (P = 0.009) in patients with serum creatinine < median. Differences NS in all other outcomes	Mean change in SUA: −2.2 mg/dL Differences NS in all other outcomes	Mean change in SUA : −2.7 mg/dL Differences NS in all other outcomes

CKD, chronic kidney disease; d, day; DKD, diabetic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; iGFR, iohexol glomerular filtration rate; RASi, inhibitors of renin–angiotensin system; SUA, serum uric acid; T1DM, type 1 diabetes mellitus; UACR, urinary albumin to creatinine ratio; UAER, urinary albumin excretion rate; yrs, years.

of 36 months, febuxostat delayed the progression of renal dysfunction (a composite of development of microalbuminuria, progression to overt albuminuria or worsening of overt albuminuria, doubling of serum creatinine or progression to ESKD), a result mainly driven by a reduced proportion of patients with a progression of albuminuria [46]. Similarly, in the PERL study, in patients with normal albuminuria, a trend in favor of allopurinol as compared with placebo was evident in contrast to what was observed in patients with increased albuminuria.

Second, the great heterogeneity of baseline uric acid level ranging from normal to very high level especially in CKD-FIX and of concomitant therapy could have largely influenced the results. Furthermore, insufficient power as a consequence of incomplete enrolment (60% of what initially planned for), a high percentage of discontinuation trial regimen (up to 25–30%), and the use of heterogeneous surrogate outcome could have confounded the results in CKD-FIX.

Interestingly, while results of RCTs do not support the use of ULT with XO inhibitors to slow the progression of CKD, one cannot help noticing that several other trials in the cardiovascular area have shown a relationship between drug-induced changes in serum uric acid and renal as well as cardiovascular outcome. Thus, for example, in the milestone RENAAL trial (Reduction of Endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan), carried out on patients with type 2 diabetes and overt nephropathy, each 0.5 mg/dL reduction in uric acid level observed with losartan (a drug with a peculiar uricosuric effect) was associated with a 6% reduction in the risk of doubling serum creatinine or progression to ESKD, suggesting that approximately one-fifth of the drug's renoprotective effect could be attributed to its effect on serum uric acid levels [47]. This post-hoc analysis provides only statistical association and does not prove causal relationship. Furthermore, the observed difference in serum uric acid between study arms was due to a rising trend over time in the placebo group rather than to a reduction of serum uric acid values in the losartan-treated group, thus adding a degree of uncertainty to interpretation of results [48]. More recently, SGLT2is, a class of antidiabetic drugs that act by promoting glycosuria at the proximal renal tubule and thereby enhance uric acid excretion through the activation of a downstream tubular glucose–urate antiporter (GLUT-9), has shown to induce reduction in uric acid levels of potential clinical benefit [49]. Results from several RCTs trials consistently indicate that changes in serum uric acid overtime account for a significant proportion of renal and cardiovascular benefit observed with SGLT2is [50–52]. Similar beneficial effect of serum uric acid changes overtime has been reported with Sacubitril–Valsartan in patients with heart failure and reduced ejection fraction although the pathogenetic mechanisms underlying this effect are still unclear [53].

CONCLUSIONS

Current evidence does not support the use of ULT with XO inhibitors to ameliorate CKD progression. However, the possibility that pharmacologic-induced changes in serum uric acid may improve renal outcome remains open due to methodological weaknesses from available trials that make results inconclusive. Furthermore, indirect evidence from several studies using some diverse cardiovascular drugs that indirectly modify serum uric acid values support a role for uric acid as a potentially modifiable cardiovascular and renal risk factor. Perhaps, further large RCTs might be carried out to evaluate whether specific subgroups of patients may benefit from urate-lowering agents in terms of nephroprotection. This could be especially important in the setting of very early and mild stages of renal damage. In addition, specific pathogenetic pathways linking changes in serum uric acid and renal damage will have to be taken into account when devising clinical trials based on recent preclinical evidence that the presence of crystalluria drives the development of CKD.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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