IJKD KIDNEY DISEASES

Allopurinol Against Progression of Chronic Kidney Disease

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Introduction. Hyperuricemia is common in approximately 50% of patients with kidney failure due to decreased uric acid excretion, and it has been recently known as an independent factor in the progression of renal insufficiency. Allopurinol inhibits the production of uric acid. The aim of this study was to evaluate the effect of allopurinol on chronic kidney disease progression.
Materials and Methods. In a clinical trial, patients with stages 3 and 4 of chronic kidney disease were divided into two groups to receive allopurinol, 100 mg, daily and placebo for 12 months. Patients' kidney function and serum uric acid levels were assessed at baseline and 3, 6, and 12 months after initial administration. Subgroups of patients with severe and mild glomerular filtration rate (GFR) impairment (GFR, 15 mL/min/1.73 m^2 to 30 mL/min/1.73 m^2 and 30 mL/min/1.73 m^2 to 60 mL/min/1.73 m^2, respectively), were compared between the groups.
Results. Serum uric acid levels decreased significantly during after 12 months of allopurinol administration ($P = .004$). In patients with severe GFR impairment, serum creatinine levels did not decrease significantly and there was no significant increase in GFR, but in those with mild GFR impairment, serum creatinine levels decreased and GFR increase significantly ($P < .001$) after administration of allopurinol. These effects were not observed in the control subgroups.
Conclusions. Allopurinol may slow down stage 3 chronic kidney disease progression and could be administered with other effective medications for controlling the kidney disease.

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INTRODUCTION

The relationship between hyperuricemia and kidney disease is known since long time ago, but it is not clear whether hyperuricemia is a risk factor or just a marker of kidney disease. Despite the increased excretion of urate through the gastrointestinal tract in patients with kidney disease, 50% of patients have hyperuricemia due to decreased uric acid excretion in the urine.[1-4] Any increase in the amount of serum uric acid augments the risk of hypertension and cardiovascular disease in these patients, as it also gives rise to an increase of acute phase proteins. Chronic hyperuricemia stimulates the renin-angiotensin system, inhibits the release of endothelial nitric oxide, causes renal vasoconstriction, and increases blood pressure. This is why high levels of uric acid may play a role in the pathogenesis of interstitial inflammation and progression of kidney disease.[5-7]

Allopurinol, as a xanthine oxidase inhibitor, inhibits the production of uric acid and then reduces serum uric acid levels. In animal models, it improves blood pressure and slows down the progression of kidney disease. Allopurinol side

effects includes allergic reaction, bone marrow suppression, and hepatotoxicity.[8-10]

Relevant to this issue is the possible role of uric acid in the development and progression of the disease, and given that allopurinol reduces the amount of uric acid, and it may decrease kidney disease progression, as well. Hence, the aim of this study was to examine the possible effects of allopurinol in reducing the progression to chronic kidney failure in patients with kidney disease and hyperuricemia.

MATERIALS AND METHODS

This study was a clinical trial. Participants were selected objectively and randomly assigned to the case and control groups. Patients were also stratified into 2 groups with severe and mild decrease in glomerular filtration rates (GFRs): 15 mL/min/1.73 m^2 to 30 mL/min/1.73 m^2 and 30 mL/min/1.73 m^2 to 60 mL/min/1.73 m^2. Duration of follow-up was 12 months. The sampling method consisted of considering the level of type I error ($\alpha = 0.05$), the power of 0.9, and information about the variations of GFR variable, used in a similar study.[11] After approval by the Research Council of Kermanshah University of Medical Sciences, this study was conducted to investigate the effect of oral allopurinol in the progression of kidney disease in patients referred to Mahdieh Clinic, Kermanshah, during 2014 and 2015.

Inclusion criteria were the presence of chronic kidney disease, a GFR below 60 mL/min/1.73 m^2 and above 15 mL/min/1.73 m^2, a uric acid level greater than 6 mg/dL, an age greater than 18 years, and no increase beyond 50% in serum creatinine level in the past 3 months. Exclusion criteria were intolerance to allopurinol, history of hypersensitivity to the drug, the possibility of pregnancy, liver disease, and gout history. Thereby, individuals in the control group were selected based on the variables listed in the demographic form (age, sex, hypertension, diabetes mellitus, etc) of the study groups.

Patients in the case group were given allopurinol, 100 mg, tablets daily for 12 months and the control group received placebo tablets. Kidney function of the participants was assessed in terms of GFR, serum uric acid level, and serum creatinine level at baseline and months 3, 6, and 12. Patients who suffered from allopurinol side effects (clinical or biochemical) were excluded from the study.

RESULTS

In this study, 214 patients with a GFR between 15 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2 were referred to the Mahdieh Clinic in Kermanshah in 2015, and enrolled the study. Nineteen patients were excluded due to drug side effects, mortality from various causes, and lost to follow-up. Overall, 196 patients (54.6% men) remained in the study as follows: 96 patients (49%) in the case group A (77 patients with mild and 19 with severe GFR impairment) and 100 patients (51%) in the control group (77 patients with mild and 23 with severe GFR impairment). Of all the participants, 119 (60.7%) patients had hypertension, 62 (31.6%) were smokers, 79 (40.3%) had diabetes mellitus, and 38 (19.4%) had hyperlipidemia. There is no significant differences between the two groups in sex distribution, hypertension, smoking, diabetes mellitus, and hyperlipidemia (Table 1).

Serum uric acid levels were not significantly different at baseline or at 3 months after administration of allopurinol between the two groups at the GFR subgroup levels, but they were significantly lower in the case subgroup of severe GFR impairment at 12 months and in the case subgroup of mild GFR impairment at 6 and 12 months, compared to their control counterparts (Table 2). There was a significant decrease in serum uric acid level during the 12-month administration of allopurinol in the case subgroup with severe GFR impairment ($P = .004$; Figure 1), but no such a significant change was observed in the control group ($P = .06$). A similar significant decrease was observed associated with allopurinol in the case subgroup of those with mild GFR impairment ($P < .001$; Figure 2).

Serum creatinine levels were not significantly

Table 1. Characteristics of Study Groups

Characteristic	Study Group		*P*
	Allopurinol	Placebo	
Sex			
Male	53 (55.2)	54 (54)	
Female	43 (44.8)	46 (46)	.87
Hypertension	55 (57.3)	64 (64)	.34
Smoking	31 (32.3)	31 (31)	.85
Diabetes mellitus	35 (36.5)	44 (44)	.85
Hyperlipidemia	18 (18.8)	20 (20)	.85

Table 2. Serum Uric Acid Levels During the Study by Severe and Mild Glomerular Filtration Rate (GFR) Impairment

Study Time	Serum Uric Acid, mg/dL		*P*
	Allopurinol Group	Placebo Group	
Mild GFR impairment			
Baseline	7.86 ± 1.36	7.77 ± 1.26	.86
3 months	6.83 ± 1.63*	7.09 ± 1.10*	.26
6 months	6.56 ± 1.69*†	7.18 ± 1.19*	.001
12 months	6.16 ± 1.44*†	7.03 ± 1.28*	< .001
Severe GFR impairment			
Baseline	7.85 ± 1.41	7.70 ± 0.95	.68
3 months	7.15 ± 1.54*	6.9 ± 1.24*	.56
6 months	7.16 ± 1.26*	7.30 ± 1.20	.71
12 months	6.36 ± 1.34*‡	7.47 ± 1.45	.02

*P < .05 compared with baseline
†P < .05 compared with 3 months
‡P < .05 compared with 6 months

different between the two groups at the subgroup levels at baseline or 3, 6, and 12 months after administration of allopurinol (Table 3). Neither allopurinol nor placebo had a significant effect on serum creatinine trend during the study in the subgroups with severe GFR impairment (P = .51 and P = .68, respectively; Figure 3). Among the subgroups with mild GFR impairment, there was a significant reduction of serum creatinine levels during the 12 months after administration of allopurinol (P < .001; Figure 4), but not after administration of placebo (P = .93).

Despite a significant different in GFR at baseline between the two subgroups with severe GFR impairment, other comparisons between the two groups were not significant (Table 4). An

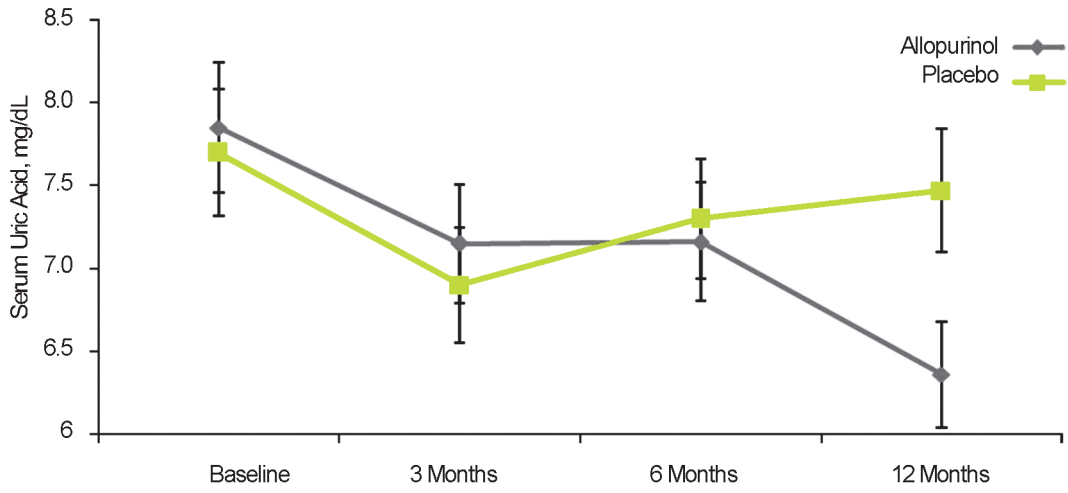

Figure 1. Average serum levels of uric acid at baseline and 3, 6, and 12 months after administration of allopurinol or placebo in patients with severe glomerular filtration rate impairment.

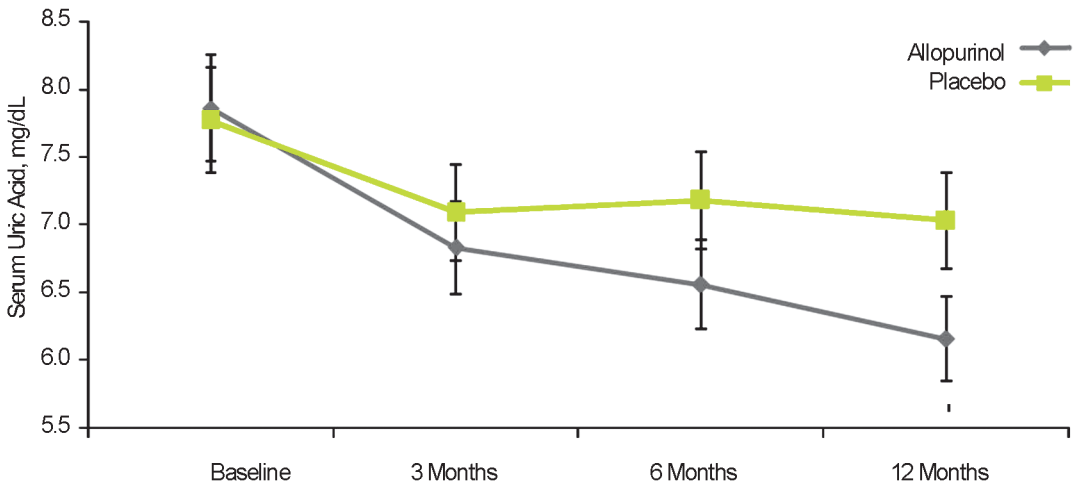

Figure 2. Average serum levels of uric acid at baseline and 3, 6, and 12 months after administration of allopurinol or placebo in patients with mild glomerular filtration rate impairment.

Table 3. Serum Creatinine Levels During the Study by Severe and Mild Glomerular Filtration Rate (GFR) Impairment

Study Time	Serum Creatinine, mg/dL		*P*
	Allopurinol Group	Placebo Group	
Mild GFR impairment			
Baseline	1.66 ± 0.30	1.68 ± 0.37	.82
3 months	1.66 ± 0.56	1.65 ± 0.40	.77
6 months	1.61 ± 0.44*	1.68 ± 0.41	.21
12 months	1.54 ± 0.41*†‡	1.66 ± 0.41	.09
Severe GFR impairment			
Baseline	3.40 ± 0.95	2.89 ± 0.56	.06
3 months	3.14 ± 1.06*	2.78 ± 0.78	.30
6 months	3.21 ± 1.31	2.74 ± 0.84	.17
12 months	3.28 ± 1.51	2.81 ± 0.91	.29

*P < .05 compared with baseline
†P < .05 compared with 3 months
‡P < .05 compared with 6 months

Table 4. Glomerular Filtration Rate (GFR) During the Study by Severe and Mild GFR Impairment

Study Time	GFR, mL/min/1.73 m^2		*P*
	Allopurinol Group	Placebo Group	
Mild GFR impairment			
Baseline	50.37 ± 11.26	50.38 ± 13.22	.67
3 months	52.47 ± 14.23	52.09 ± 15.33	.64
6 months	53.57 ± 14.31*	50.95 ± 14.92	.24
12 months	56.82 ± 16.53*†‡	51.99 ± 15.28	.08
Severe GFR impairment			
Baseline	20.84 ± 5.80	24.57 ± 3.97	.02
3 months	25.74 ± 12.01	26.87 ± 7.82	.35
6 months	27.74 ± 18.94	27.91 ± 9.09	.25
12 months	27.32 ± 16.4	27.48 ± 9.85	.54

*P < .05 compared with baseline
†P < .05 compared with 3 months
‡P < .05 compared with 6 months

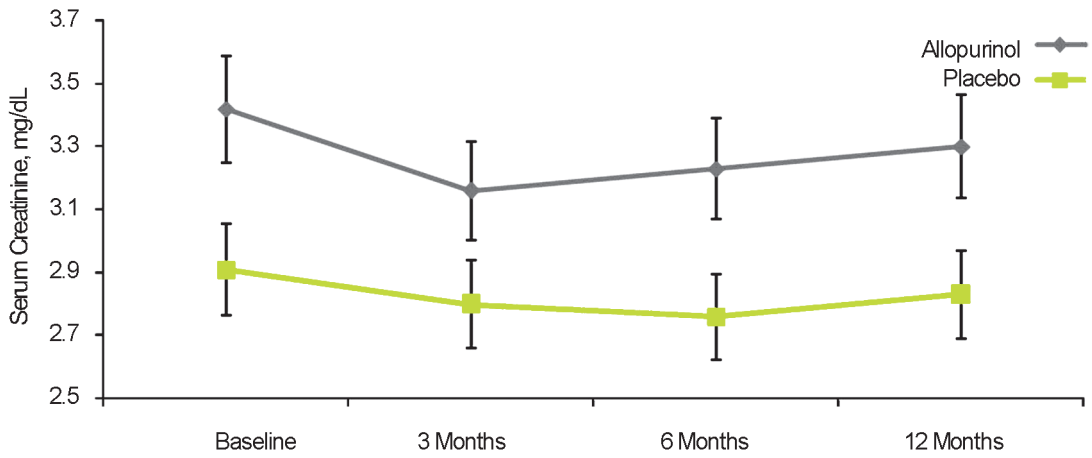

Figure 3. Average serum levels of creatinine at baseline and 3, 6, and 12 months after administration of allopurinol or placebo in patients with severe glomerular filtration rate impairment.

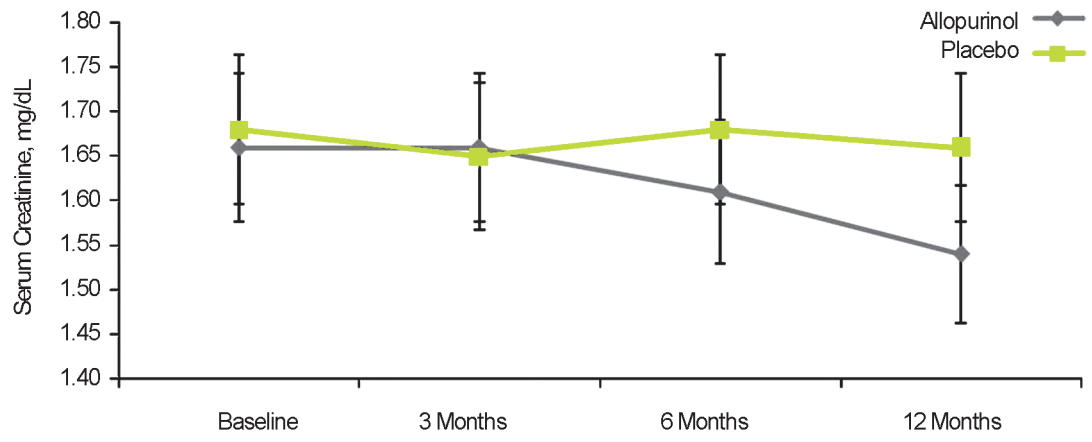

Figure 4. Average serum levels of creatinine at baseline and 3, 6, and 12 months after administration of allopurinol or placebo in patients with mild glomerular filtration rate impairment.

improvement in GFR was seen in both subgroups during the administration of allopurinol, but the improvement was significant in those with mild GFR impairment only (P < .001; Figures 5 and 6). No improvement in GFR was observed in the subgroups receiving placebo.

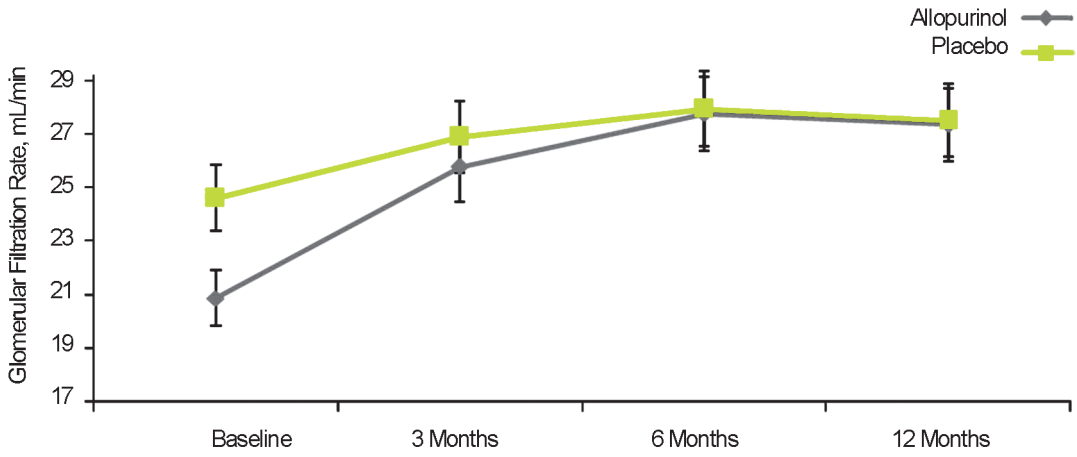

Figure 5. Average glomerular filtration rate at baseline and 3, 6, and 12 months after administration of allopurinol or placebo in patients with severe glomerular filtration rate impairment.

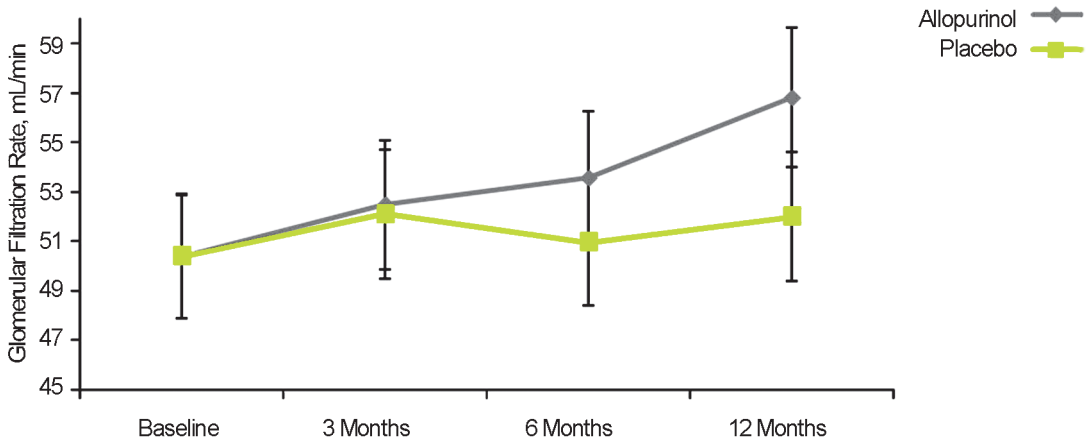

Figure 6. Average glomerular filtration rate at baseline and 3, 6, and 12 months after administration of allopurinol or placebo in patients with mild glomerular filtration rate impairment.

DISCUSSION

After administration of allopurinol for patients with a baseline GFR between 15 mL/min/1.73 m^2 and 30 mL/min/1.73 m^2, uric acid levels decreased significantly during 12 months. Uric acid levels in patients taking allopurinol was significantly less than the placebo consumers. Uric acid levels decreased significantly in patients with a baseline GFR between 30 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2 after administration of allopurinol. At 6 months and 1 year after administration of the drug, uric acid levels in patients taking allopurinol was remarkably less than placebo users. This implies that allopurinol is helpful in lowering uric acid levels of patients with kidney disease. Similarly, Goicoechea and colleagues concluded that the level of uric acid in patients with a GFR less than 60 mL/min/1.73 m^2 decreased within 24 months of taking allopurinol.[10] Siu and coworkers observed that administering allopurinol causes a reduction in uric acid level within 12 months in patients with hyperuricemia and mild to moderate chronic kidney disease.[4] Thurston and coworkers reviewed studies which had used allopurinol in the treatment of chronic kidney disease and realized that a greater number of patients with chronic kidney disease treated with allopurinol attained the expected uric acid levels, compared with those who were not under allopurinol treatment.[14] Moreover, uric acid level in hemodialysis patients taking allopurinol is lower than a control group.[15]

Bayram and colleagues concluded that in the class 2-4 renal disease, allopurinol decreases uric acid levels in the patients.[16] Osadchuk and colleagues found that uric acid levels in patients with kidney transplantation taking allopurinol

fell within 2 years and that this level was lower in this group than the control group.[17] In addition, Pai and associates realized that uric acid levels of chronic kidney disease patients with hyperuricemia, compared to baseline, was significantly reduced after 6 months, 1 year, and 2 years of treatment with allopurinol.[18] Yelken and colleagues, who also revealed similar results, reported that uric acid levels of chronic kidney disease patients with hyperuricemia dropped down significantly after 8 months of allopurinol therapy, compared with the time before treatment. However, this level increased noticeably for 8 weeks after stopping allopurinol.[19] Kanbay and coworkers realized that uric acid levels of patients with hyperuricemia with normal renal function significantly improved during 3 months of taking allopurinol.[20]

It is important to note that in this study, the level of uric acid in patients taking allopurinol with the higher baseline GFR decreased faster (at the 6th month of measurement) than that of patients whose GFR baseline was lower. This could be due to the difference in the severity of kidney damage. In the present study, the level of serum creatinine in patients with a lower baseline GFR did not decrease after administration of allopurinol; glomerular filtration rates did not increase either. Also, the levels of serum creatinine and glomerular filtration in patients taking allopurinol and placebo were the same within a year after drug administration. Hence, we can infer that allopurinol administration is no effective in reducing the levels of serum creatinine and glomerular filtration in patients with a lower baseline GFR.

Of course, in the case of patients with a higher baseline GFR, the level of serum creatinine significantly fell down after administering allopurinol for 1 year; on the other hand, GFR also increased significantly. Also, within 1 year after medication administration, the level of creatinine in patients taking allopurinol was less than that of the placebo consumers, but it was not significant. Moreover, GFR in patients taking allopurinol was higher–though not significantly–than those who took placebo. As a result, allopurinol administration may lower creatinine levels and increase glomerular filtration rates in patients with severe kidney impairment. Survey Results of previous studies demonstrate that allopurinol delays kidney disease progression as measured by serum creatinine in hyperuricemic patients with chronic kidney disease.[21] Siu and colleagues observed that serum creatinine levels in hyperuricemic patients with mild to moderate chronic kidney disease taking allopurinol display a declining trend within 12 months, although they did not see a significant difference, compared to the control group.[4] Conversely, Yelken and colleagues did not observe a significant difference in serum creatinine levels of hyperuricemic patients with chronic kidney disease at the time of consumption and stopping allopurinol for 8 weeks. This inconsistency can be related to the differences in the stages of kidney disease or patients' initial serum creatinine levels.[19] Goicoechea and colleagues found that glomerular filtration levels in patients with GFR less than 60 mL/min/1.73 m^2 increased within 24 months of allopurinol administration.[10] In the research conducted by Osadchuk and colleagues on kidney transplant patients taking allopurinol, glomerular filtration rates increased during the first year and it was higher than in the control group.[17] Pai and colleagues, similarly, stated that after 6 months, 1 year, and 2 years of treatment with allopurinol, glomerular filtration rates in hyperuricemic patients with chronic kidney disease remained stable compared to baseline, while in the placebo group it had lessened. There was also indicated an inverse relationship between uric acid and glomerular filtration rates at each period of time.[18] Kanbay and colleagues reached to similar conclusions. They suggested that glomerular filtration level of hyperuricemic patients with normal renal function improved considerably during 3 months of taking allopurinol.[20]

The exact mechanism of allopurinol effect on the progression of chronic kidney disease is unknown, but it probably depends on various factors.[18] Uric acid has many adverse effects and it can cause endothelial dysfunction that can be improved with allopurinol; it can also activate circulating platelets or disrupt endothelial nitric oxide production.[22] Various trial studies have shown that allopurinol treatment improves oxidative stress, endothelial function, and progression of chronic kidney disease.[23,24] High uric acid increases glomerular hydrostatic pressure, directly stimulate the renin-angiotensin system and leads to the proliferation of vascular smooth muscle cells in blood vessels in rats, which itself induces more rigid vessel

walls and reduces the protective mechanism and self-regulation; consequently, the arterial pressure is transferred directly to the glomeruli and, as a result of glomerular hypertrophy and sclerosis, triggers glomerular high blood pressure.[25] Hence, allopurinol, by reducing high uric acid levels, as a factor indirectly serves to reduce glomerular hydrostatic pressure and thus helps mitigate kidney damage.[18] Finally, it appears that long-term treatment with allopurinol can slow down the progression rate of renal disease.[26]

Limitations of this study included the following: first, this study was conducted for 1 year after administration of allopurinol. Designing cohort studies with longer follow-up periods can be useful. Second, the sample size was low; therefore, it is recommended that future studies be designed with larger sample sizes, especially more patients with severe kidney damage. Third, in this study, some dietary recommendations, such as protein restriction, were made to the patients, but the impact of their diet on kidney function were not explored.

CONCLUSIONS

This study proposes that prescribing a low-dose of allopurinol can be an effective drug to control uric acid levels in patients with chronic kidney disease (stages 3 and 4), as well as creatinine and glomerular filtration rates in patients with chronic kidney disease (stage 3). Thus, allopurinol can prevent the progression of kidney disease. Due to the positive effect of allopurinol in slowing down the procession of kidney disease, we suggest that this medication be administered along with other medications of chronic kidney diseases. Furthermore, it is recommended that the current study remain cohort so as to assess the impact of this treatment in the long term. Also promising can be the use of allopurinol with a dose capable of reducing serum uric acid level below 6 mg/dL, then enabling one to measure the outcome of treatment.

CONFLICT OF INTERET

None declared.

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