J Nephropharmacol. 2017; 6(2): 138–141.

http://www.jnephropharmacology.com DOI: 10.15171/npj.2017.21

Journal of Nephropharmacology

The effect of allopurinol on the progression of chronic kidney disease

Aygul Ozdemir, Ayca Inci*

Antalya Training and Research Hospital, Nephrology Department, Antalya, Turkey

ARTICLEINFO

Article Type:
Original

Article History:
Received: 10 January 2017
Accepted: 2 May 2017
ePublished: 14 May 2017

Keywords:
Chronic kidney disease
Allopurinol
Uric acid
Glomerular filtration rate
Hyperuricemia

ABSTRACT

Introduction: Hyperuricemia has been associated with the development of hypertension, cardiovascular, and renal disease.
Objectives: We conducted a prospective study to investigate the benefits of allopurinol treatment in hyperuricemic patients with chronic kidney disease (CKD) stage 3.
Patients and Methods: Our study includes a total of 132 patients (41 females and 91 males) with CKD grade 3 who are followed up by the pre-dialysis polyclinic. Around 67 of these patients administered allopurinol while 65 patients were not administered. The therapy protocol for the patients was allopurinol 150 mg/d and the duration of the follow-up was 12 months. Clinical records of the patients were screened, to start with 3, 6, 9 and 12 months, eGFR (estimated glomerular filtration rate) values were calculated.
Results: The patients' eGFR with allopurinol treatment was increased compared with baseline values. 12th month increased by 1.02 ± 8.89 mL/min/1.73 m^2 from baseline in eGFR, but it was not statistically significant ($P = 0.352$). In the control group 12th month showed a decrease in baseline GFR value of 2.59 ± 7.9 mL/min/1.73 m^2 ($P = 0.012$). The 3, 6, 9, 12th months compared with baseline in the allopurinol treatment group showed a significant decrease in uric acid value ($P < 0.05$).
Conclusion: Decreased renal progression was observed by reduction of serum uric acid levels at stage 3 hyperuricemic CKD with allopurinol. The annual decline in GFR in hyperuricemic patients, is more than normouricemic patients.

Original

Implication for health policy/practice/research/medical education:
Hyperuricemia has been associated with the development of hypertension, cardiovascular, and renal disease. We conducted a prospective study to investigate the benefits of allopurinol treatment in hyperuricemic patients with chronic kidney disease stage three and showed that with allopurinol administration annual decline in glomerular filtration rate in hyperuricemic patients, is slower than normouricemic patients.

Please cite this paper as: Ozdemir A, Inci A. The Effect of allopurinol on the progression of chronic kidney disease. J Nephropharmacol. 2017;6(2):138-142. DOI: 10.15171/npj.2017.21.

Introduction

Chronic kidney disease (CKD) is described as the presence of a renal disease lasting for more than 3 months, which is detected with biochemical analysis, urine analysis or imaging methods regardless of presence of reduced glomerular filtration rate (GFR) (1). Systemic hypertension, abnormalities of calcium-phosphate metabolism, hyperparathyroidism, intraglomerular hypertension, hyperlipidemia, acidosis, hyperuricemia and anemia are the important factors contributing to progression of chronic renal disease (2,3).

Serum uric acid level increases as urinary excretion of uric acid decreases in patients with CKD. Elevated serum uric acid level increases the risk for hypertension and cardiovascular disease development (4-6). Chronic hyperuricemia has a pathogenetic role in interstitial inflammation and renal disease progression (7). Allopurinol decreases serum uric acid levels by inhibiting xanthine oxidase enzyme. Limited number of studies conducted with hyperuricemic chronic renal disease patients indicate that allopurinol may be effective for slowing renal disease progression (8). However sufficient number of studies are not available in literature.

Objectives

In our study, we planned to investigate the effect of allopu-

***Corresponding author**: Ayca Inci, aycainci2004@hotmail.com

rinol on renal progression.

Patients and Methods

A total of 132 chronic renal disease patients (41 female, 91 male) who were aged between 18-70 years, followed up by Nephrology Department of Antalya Research and Training Hospital between March 2011-September 2012, whose estimated GFR (eGFR) was 30-60 mL/min/1.73 m^2, who had hyperuricemia (serum uric acid >7 mg/dL) were enrolled in the study. Of them, 67 were receiving allopurinol and 65 were not. Patient selection was done based on age, gender, cause of renal failure, baseline eGFR and uric acid values. Patients in both groups were on a salt restricted and protein restricted (0.6 g/kg daily) diet in the course of the study. All participants were receiving angiotensin converting enzyme inhibitor or angiotensin receptor blocker antihypertensives and alpha-ketoacid. Presence of coronary artery disease, diabetes mellitus, hypertension and vitamin D use ratios were similar in both groups. Serum blood urea nitrogen (BUN), creatinine, albumin and uric acid levels tested with 3 months of intervals and eGFR values were calculated using MDRD formula. Patients who receiving 150 mg daily allopurinol for 2 months were included in the study.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The research was approved by ethical committee of Antalya Training and Research Hospital (Antalya, Turkey).

The goals of the study were explained to participants and all of them accepted to participate and were assured the confidentiality of their individual information as well as the voluntary nature of participating in the study.

Statistical analysis

Frequency, ratio, mean, standard deviation values were used as descriptive statistics. Distribution of variables was controlled with Kolmogorov–Smirnov test. Independent samples *t* test and Mann-Whitney U test were used for analysis of quantitative data. Paired samples *t* test was used for repeated measurements. Chi-square test was used for analysis of qualitative data and Fisher's exact test was used when chi-square test did not meet the conditions. SPSS 20.0 program was used for analysis. A *P* value less than 0.05 was considered being statistically significant.

Results

Demographic and laboratory characteristics of treatment and control groups are shown in Table 1. One hundred thirty-two patients with stage 3 CKD were incorporated to the investigation. Mean age was 54.57 ± 13.68 years in allopurinol-receiving group and 56.38 ± 12.8 years in control group ($P = 0.429$). Treatment group consisted of 19 females (28.4%), 48 males (71.6%); control group consisted of 22 females (33.8%) and 43 males (66.2%) ($P = 0.496$). Mean duration of follow up was 12.03 ± 1.56 months in treatment group and 12.08 ± 1.50 months in control group ($P = 0.651$).

Table 1. Demographic characteristics of the patients[a]

	Allopurinol group (n = 67)	Control group (n = 65)
Age (y)	54.57±13.68	56.38±12.58
Male/Female	48/19	43/22
Renal pathology, No. (%)		
Diabetes	22 (32.8)	17 (26.2)
Hypertension	30 (44.8)	26 (40)
Polycystic renal disease	2 (3)	2 (3.1)
Nephrolithiasis	3 (4.5)	1 (1.5)
CGN/CTIN	9 (13.4)	12 (18.5)
Unknown	1 (1.5)	7 (10.8)
Medications, No. (%)		
ACE inhibitor /ARB	67 (100)	65 (100)
Vitamin D	25 (37.3)	24 (36.9)
Diuretic	33 (49.1)	34 (52.7)
Thiazide	25	27
Furasemid	0	1
Follow up (month)	12.03±1.56	12.08±1.50

No significant differences were observed between the different analyzed variables.

Twenty-five patients (37.3%) in treatment group and 27 patients (41.5%) in control group were receiving thiazide group diuretics ($P = 0.726$). No difference was detected between the patients who were receiving or not receiving allopurinol treatment with respect to age, gender, duration of follow up, ratios of vitamin D and diuretic administration, coronary artery disease, diabetes mellitus, hypertension ($P > 0.05$).

Both in the groups treated or not-treated with allopurinol; baseline eGFR, 3rd month eGFR, 6th month eGFR, 9th month eGFR and 12th month eGFR were calculated. A reduction was not detected in eGFR value beginning from 3rd month compared to baseline value in allopurinol-receiving group. eGFR value increased 1.02±8.9 mL/min/1.73 m2 on month 12 compared to baseline value however, the difference was not statistically significant ($P = 0.352$). In control group, eGFR decreased beginning from month 3 compared to baseline value. eGFR value decreased 2.59±7.9 ml/min/1.73 m^2 on month 12 compared to baseline value and the difference was statistically significant ($P = 0.012$) (Table 2).

There was not a significant difference between baseline uric acid levels of the patients receiving allopurinol or not ($P > 0.05$). Serum uric acid values on months 3, 6, 9 were significantly higher in control group compared to the ones receiving allopurinol ($P < 0,05$). Serum uric acid values significantly decreased on months 3, 6, 9 and 12 compared to baseline values in allopurinol-receiving group ($P < 0.05$). A reduction of 2.09 ± 1.12 mg/dL was detected at the end of month 12 compared to baseline values and the difference was statistically significant ($P < 0.001$) (Table 3).

Discussion

Elevated serum uric acid level was found to be associated

Table 2. eGFR change in allopurinol and control group

eGFR (mL/min/1.73 m²)	Allopurinol group	Control group	P[a]
Baseline	39.97±8.12	40.07±8.36	0.945
3rd month	40.18±8.78	38.43±9.11	0.264
6th month	40.03±10.11	37.88±9.20	0.205
9th month	40.38±10.00	37.43±10.50	0.101
12th month	40.98±10.47	37.60±10.42	0.067
Baseline/3rd month change	0.21±6.31	-1.64±6.35	0.096
Baseline/6th month change	0.06±8.10	-2.19±7.41	0.099
Baseline/9th month change	0.41±8.10	-2.64±7.48	0.027
Baseline/12th month change	1.2±8.89	-2.59±7.90	0.016

[a] $P < 0.05$.

Table 3. The effect of allopurinol treatment on uric acid level

	Allopurinol group	Control group	P[a]
Baseline	8.04±0.72	8.15±0.97	0.429
3rd month	6.44±1.02	7.62±1.43	0.000
6th month	6.08±1.07	7.99±1.23	0.000
9th month	5.94±1.05	7.74±0.95	0.000
12th month	5.94±1.13	7,82±1.22	0.000
Baseline/3rd month change	-1,59±1.00	-0.53±1.26	0.000
Baseline/6th month change	-1.95±1.11	-0.17±1.20	0.000
Baseline/9th month change	-2.10±1.18	-0.42±1.12	0.000
Baseline/12th month change	-2.09±1.12	-0.35±1.28	0.000

[a] $P < 0.05$.

with increased hypertension and cardiovascular disease risk (9-11). Hyperuricemia was detected to have a pathogenetic role in renal disease progression. Serum uric acid level was shown to be a predictor for renal progression in patients with IgA nephropathy (12,13). Elevated uric acid level was shown to be correlated with renal failure development also in type 2 diabetic patients with normal renal function (14). Allopurinol decreases serum uric acid level by inhibiting xanthine oxidase enzyme. In experimental animal models, hyperuricemia-induced functional and structural injury regressed with allopurinol treatment (15,16).

In animal models, hyperuricemia was shown to increase vasculopathy through impairing blood pressure control, increasing proteinuria, glomerulosclerosis and tubulointerstitial fibrosis (7). It was reported that reduced serum uric acid levels improved renal functions and slowed down renal disease progression. Although the mechanism of allopurinol's slowing down renal progression is not known, many factors are considered to be effective. Afferent arterioles are known to increase proliferation in vascular smooth muscle cells, lead to hardening of vessel wall and impair auto-regulatory protective mechanisms. Arterial pressure directly reflects to glomerulus and this leads to glomerular hypertension, glomerular hypertrophy and sclerosis (15). Allopurinol indirectly decreases hydrostatic pressure by reducing serum uric acid level and helps to prevent renal injury.

Uric acid has recently begun to be defined as a mediator for renal disease and its progression. Hyperuricemia leads to elevated blood pressure, kidney afferent arteriopathy, strengthened glomerular hydrostatic pressure and renal scar formation. Studies have indicated that renal dysfunction was slowed down by reducing systolic blood pressure through reducing serum uric acid levels (8). We analyzed stage 3 CKD patients who were followed up at our predialysis clinic, who had hyperuricemia and used allopurinol. We obtained similar data with literature when we compared hyperuricemic control group who were not receiving allopurinol and one year GFR changes. An increase of 1.02±8.89 mL/min/1.73 m² was detected in GFR values compared to baseline values at the end of 12.3 ± 1.56 months of follow up period ($P = 0.352$). In control group, GFR values were seen to decrease 2.59±7.9 mL/min/1.73 m² at the end of follow up period ($P = 0.012$). We may state that allopurinol treatment has a positive effect on renal function as a significant decrease was detected in GFR in non-treated group.

Fifty-four hyperuricemic patients with mild to moderate CKD were included in a small randomized-controlled study conducted by Siu et al (8). Treatment group was started 100-200 mg daily allopurinol based on baseline renal functions (200 mg daily allopurinol if creatinine is equal to or below 1.7 mg/dL and 100 mg daily allopurinol if creatinine is above 1.7 mg/dL). Basal serum creatinine levels were similar in both groups and 1.64 ± 0.63 mg/dL in treatment group, 1.86 ± 0.69 mg/dL in control group. A significant difference was not detected in creatinine level at the end of 12 months in allopurinol group(1.99 ± 0.92 mg/dL). Serum creatinine levels were seen to impair in control group at the end of the study (2.89 ± 0.96 mg/dL). A total of 113 patients with GFR<60 ml/min were included in the prospective randomized study of Goicoechea et al (17). Fifty-seven patients were administered allopurinol

100 mg daily, remaining 56 patients continued their routine treatment. Clinical, biochemical and inflammatory indices were assessed at the beginning and on months 6, 12 and 24. Renal disease progression, cardiovascular events and hospitalization with any reasons were evaluated. Serum uric acid and CRP values were seen to decrease significantly in allopurinol-treated group. In our study, serum uric acid levels were seen to decrease 2.09 ± 1.12 mL/min/1.73 m^2 at the end of 12 months compared to baseline values. Serum uric acid levels on months 3, 6, and 9 were significantly higher in the group not receiving allopurinol compared to allopurinol-receiving group.

The study of Kanbay et al (18) showed that endothelial dysfunction, blood pressure, GFR and inflammatory markers may improve with reducing uric acid using allopurinol in patients with asymptomatic hyperuricemia. Asymptomatic hyperuricemic patients without gout and 30 normouricemic control patients were included in 4 months of prospective study. Thirty hyperuricemic patients were given allopurinol 300 mg daily, 37 hyperuricemic patients were compared with 30 normouricemic patients. Basal and month 4 eGFR, blood pressure, protein/creatinine ratio in spot urine and hsCRP measurements were done. Age, gender, baseline lipid profile, eGFR, hemoglobin, glucose and proteinuria levels were found similar in three groups. CRP levels were high in hyperuricemic patients compared to normouricemic patients, as expected. Allopurinol treatment led to a decrease in serum uric acid value and systolic blood pressure and an increase in eGFR value .

In the prospective cohort study of Bellomo et al (19) conducted with 900 healthy normotensive adults (153 females, 747 males), eGFR levels were seen to decrease with increasing uric acid level. At the end of mean 59 months of follow up, GFR was shown to regress to 88±14 mL/min/1.73 m^2 from 97±16 mL/min/1.73 m^2. High serum uric acid levels were seen to be associated with GFR reduction both in females and males. Serum uric acid levels were shown to be a risk factor for the reduction in renal functions also in healthy normotensive individuals. In another retrospective cohort study conducted with 183 chronic renal disease patients, allopurinol receiving group (100 mg daily) and untreated group were compared. Blood pressure was detected to be lower on months 6, 1 and 2 years compared to baseline in allopurinol-receiving group. An inverse correlation was detected between serum uric acid level and months 6, 1 and 2 year eGFR. It was concluded that allopurinol treatment reduced uric acid and led to better blood pressure control and reduced renal disease progression in hyperuricemic chronic renal disease patients (20). Using data of modification of diet in renal disease (MDRD), uric acid was shown to be associated with all causes of mortality and cardiovascular mortality in diabetic stage 3-4 chronic renal disease patients (21). In a study conducted with a new xanthine oxidase inhibitor —febuxostat— uric acid and creatinine levels were tested before and after treatment in 60 chronic renal disease patients of whom 67% had an eGFR <30 mL/min/1.73 m^2. Uric acid levels effectively decreased with febuxostat treatment and a progressive reduction of eGFR values decreased (22).

Conclusion

In conclusion, we showed that we could slow down renal disease progression with allopurinol treatment in hyperuricemic stage 3 CKD patients. However our study has some limitations like having small number of patients and non-randomized trial. Larger, multi-center, prospective studies are required in order to better understand the positive effects of allopurinol in hyperuricemic patients.

Limitations of the study

This study was conducted on a small group of patients. We suggest larger studies on this subject.

Authors' contribution

AO: study design, data collection and statistical analysis; AI: study design and manuscript reviewing.

Conflicts of interest

The results presented in this paper have not been published previously in whole or part, except in abstract format. We certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study was supported by a grant from Antalya Training and Research Hospital. It was the thesis of Aygul Ozdemir, MD.

References

1. National Kidney Foundation. K/DOQI clinical practise guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39:S1-266.
2. Yu HT. Progression of chronic renal failure. Arch Intern Med. 2003;163:1417. doi: 10.1001/archinte.163.12.1417
3. Hebert LA, Greene T, Levey A, Falkenhain ME, Klahr S. High urine volume and low urine osmolality are risk factors for faster progression of renal disease. Am J Kidney Dis. 2003;41:962. doi: 10.1016/S0272-6386(03)00193-8
4. Süleymanlar G, Serdengeçti K, Altiparmak MR, Jager K. Trends in renal replacement theraphy in Turkey, 1996-2008. Am J Kidney Dis. 2011;57:456-65. doi: 10.1053/j.ajkd.2010.12.007.
5. Edwards NL. The role of hyperuricemia and gout in kidney and cardiovasculer disease. Clev Clin J Med Suppl. 2008;5:S13-6.
6. Gagliardi A, Miname M, Santos R. Uric acid: a marker of increased cardiovascular risk. Atherosclerosis 202:11-17, 2009. doi: 10.1016/j.atherosclerosis.2008.05.022.
7. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J,

Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183-90. doi: 10.1161/01.HYP.0000069700.62727.C5.
8. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis. 2006;47:51-9. doi: 10.1053/j.ajkd.2005.10.006.
9. Selby JV, Friedman GD, Qesenberry CP Jr. Precursors of essential hypertension:Pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. Am J Epidemiol. 1990;131:1017-27.
10. Jossa F, Farinaro E, Panico S, Krogh V, Celentano E, Galasso R, et al. Serum uric acid and hypertension: The Olivetti heart study. J Hum Hypertens. 1994;8:677-81.
11. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality: The NHANES I epidemiologic folow-up study, 1971-1992. National Health and Nutrition Examination Survey. JAMA. 2000;283:2404-10.
12. Syrjanen J, Mustonen J, Pasternack A. Hypertriglyceridemia and hyperuricaemia are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant. 2000;15:34-42.
13. Ohno I, Hosoya T, Gomi H, Ichida K, Okabe H, Hikita M. Serum uric acid and renal prognosis in patients with IgA nephropathy. Nephron. 2001;87:333-9.
14. Bo S, Cavallo-Perin P, Gentile L, Repetti E, Pagano G. Hypouricemia and hyperuricemia in type 2 diabetes: Two different phenotypes. Eur J Clin Invest. 2001;31:318-21.
15. Sánchez-Lozada LG, Tapia E, Santamaría J, Avila-Casado C, Soto V, Nepomuceno T, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney Int. 2005;67:237-47. doi: 10.1111/j.1523-1755.2005.00074.x.
16. Nakagawa T, Mazzali M, Kang DH, Kanellis J, Watanabe S, Sanchez-Lozada LG, et al. Hyperuricemia causes glomerular hypertrophy in the rat. Am J Nephrol. 2003;23:2-7.
17. Goicoechea M, Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincon A, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol. 2010:5(8):1388-93. doi: 10.2215/CJN.01580210.
18. Kanbay M, Huddam B, Azak A, Solak Y, Kadioglu GK, Kirbas I, et al. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. Clin J Am Soc Nephrol. 2011;6:1887-94. doi: 10.2215/CJN.11451210.
19. Bellomo G,Venanzi S, Verdura C, Saronio P, Esposito A, Timio M. Association of uric acid with change in kidney function in healthy normotensive individuals. Am J Kidney Dis. 2010;56:264-72. doi: 10.1053/j.ajkd.2010.01.019.
20. Pai BH, Swarnalatha G, Ram R, Dakshinamurty KV. Allopurinol for prevention of progression of kidney disease with hyperuricemia. Indian J Nephrol. 2013;23:280-6. doi: 10.4103/0971-4065.114499.
21. Madero M, Sarnak MJ, Wang X, Greene T, Beck GJ, Kusek JW, et al. Uric acid and long-term outcomes in CKD. Am J Kidney Dis. 2009;53:796-803. doi: 10.1053/j.ajkd.2008.12.021.
22. Sakai Y, Otsuka T, Ohno D, Murasawa T, Sato N, Tsuruoka S. Febuxostat for treating allopurinol-resistant hype ruricemia in patients with chronic kidney disease. Ren Fail. 2014;36:225-31. doi: 10.3109/0886022X.2013.844622.