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Outcome of Febuxostat treatment in hyperuricemic pre-dialysis chronic kidney disease patients

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Abstract

Introduction: Hyperuricemia is a cause and effect of chronic kidney disease (CKD), accelerates its progression and predisposes to acute kidney injury. Present study aimed to find out the outcome of Febuxostat treatment in hyperuricemic pre-dialysis CKD patients.

Method: This was a cross sectional study conducted in Nephrology department, Bir hospital, Nepal, during from February 2019 to January 2020, among pre-dialysis CKD stage 3-5 non dialysis (ND) patients with serum uric acid (SUA) >7 mg/d L who were treated with Febuxostat 40 mg once a day and followed up at one, two and three months. The baseline SUA, creatinine, estimated glomerular filtration rate (eGFR) calculated by the modification of diet in renal disease (MDRD) equation compared with values at follow up and according to CKD stages. The adverse effects and liver enzymes were recorded.

Result: There were total 50 patients, mean age 54.2±16.5 years, male 31 (62%). There were significant reductions of SUA from baseline of 8.9±1.4 to 7.1±1.2 vs 5.9±0.9 vs 4.7±1.0) at one, two and three month respectively, p=0.000 and increment of eGFR (ml/min/1.73m^2) from 29.6±15.0 to 31.6±16.0, 33.6±16.6, 34.1±17.1, p=0.000 and 41 (82%) patients achieved uric acid < 6mg/dl at three month. Significant reduction of uric acid in all CKD stages and increment of eGFR in CKD stage 3 and 4 were observed. Adverse effects were epigastralgia in 5 (10%) and joint pain in 13 (26%).

Conclusion: Febuxostat is an effective SUA lowering drug in pre-dialysis chronic kidney disease patients with improvement of kidney function.

Keywords: hyperuricemia, chronic kidney disease (CKD), dialysis, Febuxostat, uric acid

Introduction

Chronic Kidney disease (CKD) and hyperuricemia are interrelated. The CKD results in hyperuricemia due to decreased excretion of uric acid.[1] Hyperuricemia results and accelerates the progression of CKD and acute kidney injury (AKI) by mechanisms beyond urate crystal deposition.[2-4]

Hyperuricemia is defined as a serum uric acid (SUA) concentrations that exceeds the limit of solubility (7.0mg/dl).[5] It is associated with greater incidence of end stage renal disease and increased risk of AKI.[6,7] In CKD patients with hyperuricemia, allopurinol is effective in lowering SUA with stable kidney function.[8] However, Febuxostat is superior with significantly increased eGFR (estimated glomerular filtration rate) and longer renal survival time than allopurinol .[9, 10]

With newer evidences, hyperuricemia in CKD is treated with Febuxostat in our department. So, present study aimed to find out the outcome of Febuxostat treatment in pre-dialysis CKD patients and its effect on SUA and kidney function.

Method

This was a cross sectional study carried out in Department of Nephrology, Bir Hospital from February 2019 to January 2020 after approval from Institutional Review Board (IRB), National Academy of Medical Sciences (NAMS), Kathmandu, Nepal. Established CKD patients with eGFR<60 ml/min/1.73 m^2 (CKD stages 3 to 5, ND) and uric acid >7 mg/dl were included. The exclusion criteria were raised liver enzymes (ALT and AST greater than twice the upper limit of laboratory reference range), acute kidney injury, renal transplant recipient, CKD on dialysis, history of malignancy, hypersensitivity to Febuxostat, on drugs like azathioprine, mercaptopurine hydrate, allopurinol, vidarabin and didanosine, pregnant lady, lactating mother and planning for pregnancy during the study period.

Patients were explained about the investigational nature of the study and informed written consent was taken before enrollment. Detail history and physical examination was done and advised for baseline routine investigations including fasting blood sugar, blood urea, serum creatinine, sodium, potassium, liver enzymes, SUA, calcium, phosphorus, total protein, albumin, urine routine examination and ultrasound abdomen and pelvis both for confirmation of cause of CKD and hyperuricemia and exclusion of patients with exclusion criteria.

Predesigned pro-forma was used for data collection. Patient's age, gender, serum creatinine, uric acid and liver enzymes (AST) were recorded. Patients with SUA >7mg/dl was prescribed Febuxostat 40 mg once a day at bed time and explained about the possibility of adverse effects like skin rashes, epigastralgia, vomiting, myopathy, joint pain and hepatotoxicity that will be diagnosed by liver enzyme estimation on follow up. All patients were followed up after 1, 2 and 3 months with investigation reports of serum creatinine, uric acid and AST and adverse effects were inquired and recorded. The dose of Febuxostat was increased to 80 mg per day with persistent hyperuricemia of >8 mg/dl on follow up after one month.

The eGFR was calculated by using abbreviated MDRD (modification of diet in renal disease) equation 186 × (creatinine/88.4) - 1.154 × (age) –0.203 × (0.742 if female) × (1.210 if black) [11] and CKD staging was done as per KDIGO guideline.[12]

The data were entered in SPSS data sheet and inferential statistics was obtained by using SPSS software package. Data for continuous variables were expressed as mean ± standard deviation. Paired t-test was used to compare the mean difference before and after treatment and independent t test to compare uric acid level between patients with 40 mg and 80 mg of Febuxostat dose. Pearson correlation was used to see the relation between uric acid and eGFR.

Result

Total fifty CKD patients with eGFR < 60 ml/min/1.73m^2 and not on dialysis were studied. The causes of CKD were hypertensive nephrosclerosis (n=19), chronic glomerulonephritis (n=18), diabetic nephropathy (n=7), obstructive uropathy (n=4), chronic interstitial nephropathy (n=1) and autosomal dominant polycystic kidney disease (n=1).

The mean age (years) of patients was 54.2±16.5 (range 15-84) and 31 (68%) were male. The number of patients in CKD stage 3, 4 and 5 ND were 24 (48%), 16 (32%) and 10 (20%) respectively.

Twelve (24%) patients with SUA > 8 mg/dl were prescribed Febuxostat 80 mg per day on follow up at one month and continued till the end of study.

Febuxostat therapy had significantly and steadily decreased SUA (p=0.000) from baseline at one month, two month and three months. The SUA also decreased significantly in all CKD stages, Table 1.

Reduction of SUA to <7 mg/dl was achieved in (44%, 82% and 94%) and <6 mg/dl in (10%, 44% and 82%) at one, two and three months respectively, Figure 1 and SUA <6 mg/dl at three month was found in 87.5% of CKD stage 3, 62.5% of CKD stage 4 and 100% of CKD stage 5.

There was significant difference of mean uric acid level between patients with Febuxostat 40 mg and 80 per day at baseline (8.5 ±1.2 vs 10.1±1.3 p =0.000), one month (6.6 ±0.7 vs 8.8±0.6, p=0.000), two month (5.6 ±0.7 vs 7.0 ±05, p=0.000) and three month (4.4 ±0.5 vs 5.9±1.2, p=0.001) respectively.

Febuxostat therapy had increased calculated eGFR (p=0.000) from baseline at one month, two month and three months, Figure 2. But on evaluating the eGFR in CKD stages, the significant increase of eGFR was present only in CKD stage 3 and stage 4 with insignificant improvement in CKD stage 5ND from baseline value at 1, 2 and 3 months as shown in Table 2. By the end of 3 months therapy, 6 (25%) of CKD stage 3, 4 (25%) of CKD stage 4 and 2 (20%) of CKD stage 5 had improved to CKD stage 2, CKD stage 3 and CKD stage 4 respectively, Table 3.

The Pearson correlation between uric acid and eGFR at baseline and follow up had shown insignificant negative correlation.

The reported adverse effects were epigastralgia in 5 (10%) patients at 1 month and joint pain in 6 (12%) and 7 (14%) patients at 1 month and 2 months respectively. Liver enzymes were normal in all patients (19.0 ±3.0 vs 18.2±6.1 vs 19.1±5.1 vs 19.6±4.3) at baseline and follow up at one, two and three months respectively.

Table 1. Baseline and follow up serum uric acid after Febuxostat treatment in hyperuricemic pre-dialysis chronic kidney disease patients (N=50)

		Total (N=50)	CKD Stage 3 (N=24)	CKD stage 4 (N=16)	CKD stage 5 (N=10)
Baseline		8.9±1.4	8.7±1.1	9.5±1.7	8.6±1.4
1 month		7.1 ±1.2	6.9 ±1.0	7.48 ±1.16	7.1±1.4
2 months		5.9 ±0.9	5.6 ±0.9	6.37 ± 0.8	6.0± 0 .8
3 months		4.7 ±1.0	4.4 ±0.9	5.2 ±1.2	4.7± 0.4
p value*		0.000[!,~,#]	0.000[!,~,#]	0.001[!] 0.000[~,#]	0.004[!] 0.000[~,#]
Final SUA	< 6	41 (82%)	21 (87.5%)	10 (62.5%)	10 (100%)
	>6	9 (18%)	3 (12.5%)	6 (37.5%)	0 (0%)

CKD: (Chronic Kidney Disease)

*Paired t test, [!]baseline versus 1 month, [~]baseline versus 2 month, [#]baseline versus 3 month

Table 2. Serum Creatinine and eGFR of patients at baseline and follow-up

Variables		Baseline	1 month	2 months	3 months	p value*
Serum Creatinine (mg/dl)	Total (n=50)	2.9±1.7	2.7±1.7	2.6±1.7	2.6±1.8	0.031[!], 0.001~, 0.002[#]
	Stage 3 (n=24)	1.7±0.3	1.6±0.3	1.6±0.3	1.5±0.3	0.000[!,~,#]
	Stage 4 (n=16)	3.0±0.6	2.8±0.5	2.6±0.4	2.6±0.5	0.033[!], 0.000[~,#]
	Stage 5 (n=10)	5.7±1.9	5.4±1.9	5.1±2.3	5.2±2.6	NS[!,~,#]
eGFR (ml/min/1.7m^2)	Total (n=50)	29.6±15.0	31.6±16.0	33.6±16.6	34.1±17.1	0.000[!,~,#]
	Stage 3 (n=24)	42.7±8.9	45.3±9.0	47.5 ± 11.1	48.7±11.1	0.000[!,~,#]
	Stage 4 (n=16)	22.0±4.3	23.6±0.5	25.9±5.2	25.6±5.3	0.023!, 0.000[~,#]
	Stage 5 (n=10)	10.2±2.5	11.4±4.9	12.6±5.3	12.7±5.8	NS[!,~,#]

*Paired t test, [!]baseline versus 1 month, ~baseline versus 2 month and [#]baseline versus 3 month, NS= Not significant

Table 3. Improvement of CKD stage after Febuxostat treatment at three months

Baseline CKD stage	CKD stage at three months of Febuxostat treatment			
	Stage 2 N (%)	Stage 3 N (%)	Stage 4 N (%)	Stage 5 N (%)
Stage 3 (N=24)	6 (25%)	18 (75%)	0	0
Stage 4 (N=16)	0	4 (25%)	12 (75%)	0
Stage 5 (N=10)	0	0	2 (20%)	8

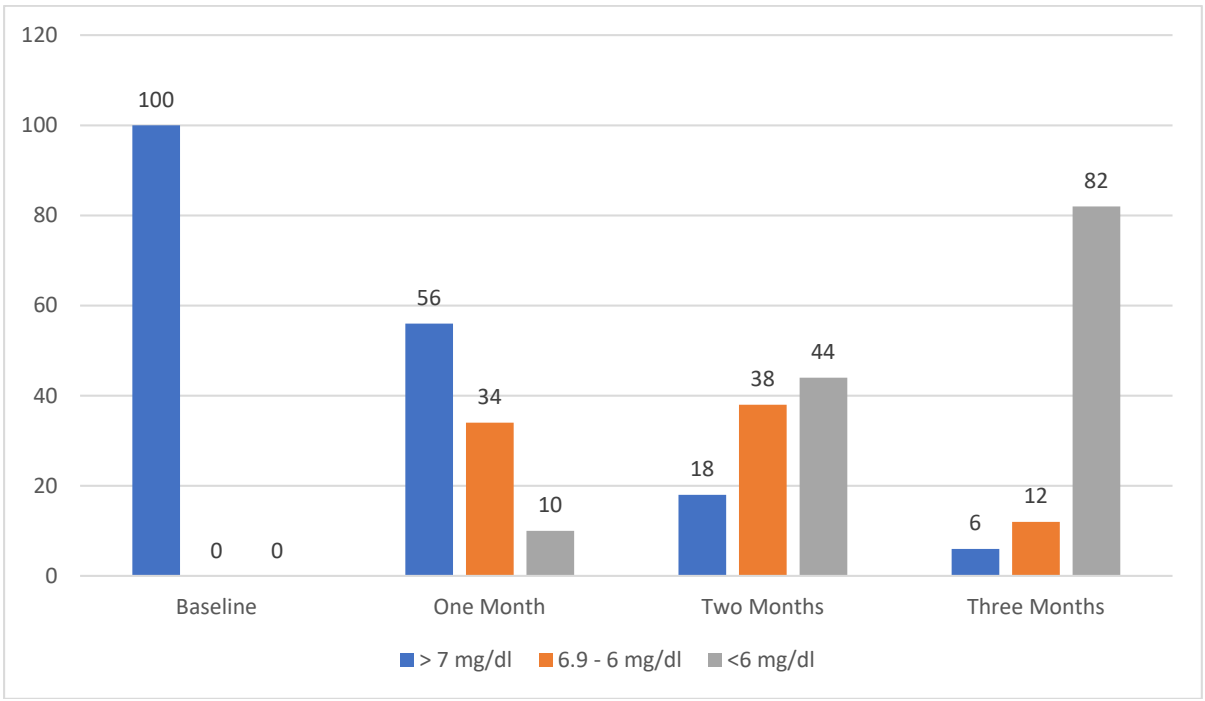

Figure 1. Grouping of patients according to serum uric acid level at one month, two months and three months

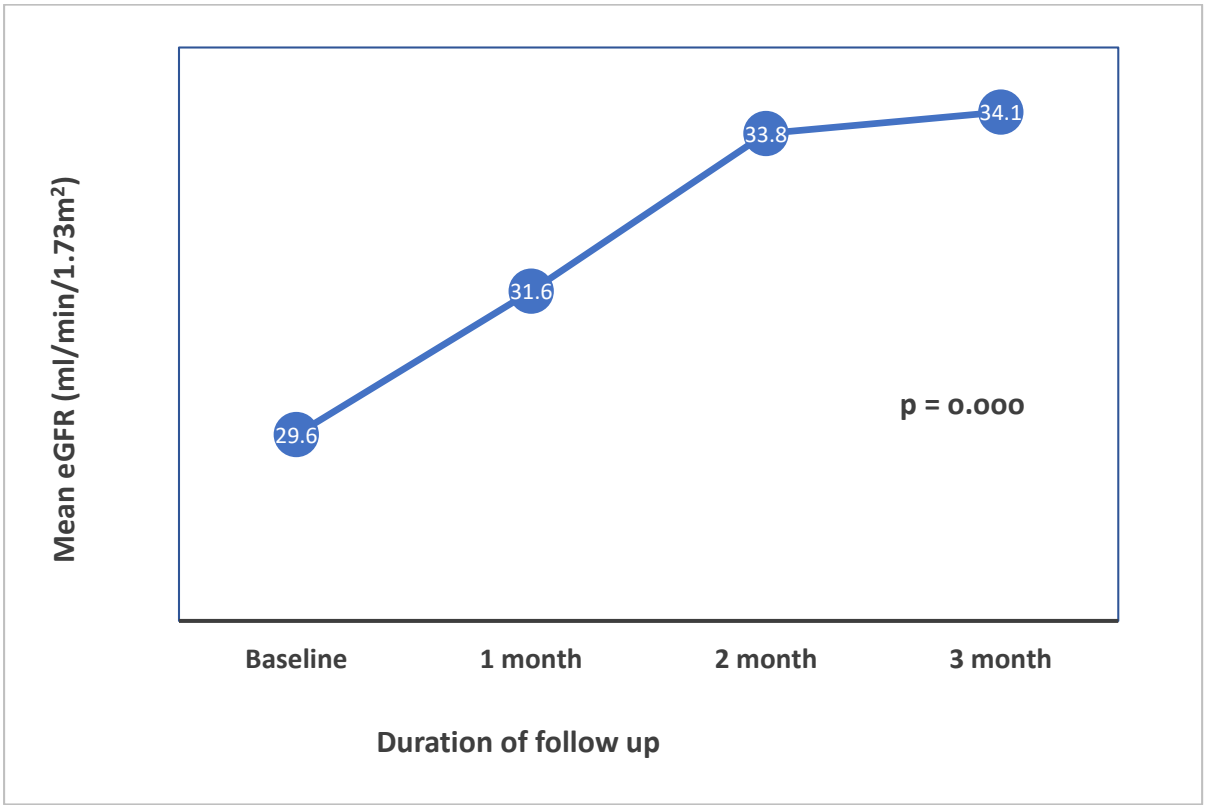

Figure 2. Mean estimated glomerular filtration rate of patients at baseline and follow up

Discussion

Our study demonstrated that SUA lowering effect of Febuxostat in hyperuricemic pre-dialysis CKD is effective in all CKD stages. The significant reduction was observed at one month of therapy itself and continued till 3 months, the end of study. Febuxostat is a novel and potent nonpurine-selective inhibitor of xanthine oxidase metabolized in the liver, is safe for patients with low eGFR without dose modification.[13] Similar results of Febuxostat were also reported in a randomized controlled trial in Japan in patients with CKD stage 3.[14] It was also reported in a retrospective analysis of CKD stage 4 and 5 (ND and on dialysis) in Taiwan on comparing SUA before and after 12 weeks treatment with Febuxostat.[15] A meta-analysis has shown the beneficial effect of Febuxostat compared to control (placebo or allopurinol) from one month to six months, but no difference on 12th month of therapy.[16]

Although hyperuricemia is defined as SUA >7 mg/dl[12], the target SUA level had been <6 mg/dl in order to decrease gouty attack by inhibiting formation of new monosodium urate crystals and promoting dissolution of existing crystals in the joints and soft tissues.[17] The 2016 European League Against Rheumatism (EULAR) had recommended the target of urate lowering treatment should be to achieve SUA <6 mg/dl in all gouty patients.[18] However, the efficacy of Febuxostat in lowering SUA in asymptomatic hyperuricemia in CKD was also evaluated with same target value. Efficacy of Febuxostat therapy have been reported in 58.1% patients with advanced CKD[15], in 76.4% patient on chronic hemodialysis[19] and in 82% patients with CKD stage 3b-5 at 12th week[20]. We found higher efficacy in82% of patients who achieved SUA <6mg/dl by the end of study period of 3 months. On further analyzing, it was found that in 87.5% of CKD stage 3, 62.5% of CKD stage 4 and 100% of CKD stage 5, indicating Febuxostat is an effective SUA lowering drug in pre-dialysis CKD patients

irrespective of degree of renal impairment. However, efficacy of drug could be dose dependent. In present study, daily dose was increased to 80 mg in 24% patients who had persistent SUA >8 mg/dl after one month of initial daily dose of 40mg therapy. The mean SUA was always significantly higher in patients with higher dosage justifying the treatment Out of 82% patients with SUA <6 mg/dl, 74% of patients were receiving 40 mg daily showing its efficacy even in low dose.

Hyperuricemia is an independent risk factor for development and progression of CKD and AKI.[21,22] Modest hyperuricemia in experimental rat models have shown exacerbated renal progression with higher BP, greater proteinuria and severe glomerulosclerosis, interstitial fibrosis and arteriolosclerosis.[3] Population based studies have also shown renal impairment in people with normal renal function and baseline hyperuricemia on follow up.[23,24] Treatment with uric acid lowering drugs (allopurinol, Febuxostat and probenecid) in CKD have shown to decrease the risk of renal failure events by 55% compared to standard treatment or placebo.[25] Febuxostat has shown to maintain significantly higher mean eGFR values consistently for 4 years compared to allopurinol and control in patients with CKD stage 3.[10] But, no difference of eGFR after 12 weeks therapy in CKD stage 4 and 5.[15]

In our study, we found significant improvement of eGFR after one month and it continued till the end of study period. However, subgroup analysis had shown the significant increment of eGFR only in CKD stage 3 and 4 and insignificant increment in CKD stage 5. In a meta-analysis, Lin TC et al have shown similar results with improvement of eGFR with Febuxostat only in subgroup analysis of patients with CKD stage 3 and 4 and no improvement when compared with control.[26] No difference in eGFR slope per year between Febuxostat and placebo therapy in CKD was reported in a randomized controlled trial.[14] However, there are also reports showing improvement of eGFR with Febuxostat in CKD and significantly low prevalence of >10% decline of eGFR over 6 months than placebo.[27] After three months of Febuxostat treatment, the improvement of eGFR in our patients translated in to increment of CKD stage from baseline in 25% of CKD stage 3 and 4 and 20% of CKD stage 5 supporting that significant reduction of SUA in hyperuricemic CKD is reno-protective and associated with significant improvement of eGFR. Studies have shown the linear inverse relationship of SUA with eGFR in patients with rheumatoid arthritis and in patients with CKD after allopurinol therapy.[28,8] However, SUA and eGFR in our patients showed no significant negative correlation both at baseline and follow up.

The Confirmation of Febuxostat in Reducing and Maintaining Serum Urate (CONFIRMS) trial have demonstrated the side effects of Febuxostat in patients with CKD were diarrhea, upper respiratory tract infection, rash and mildly raised liver enzymes and similar to patients without CKD.[29]However, Febuxostat treated patients had higher rates of acute gout flares than those treated with allopurinol which could be due to the rapid reduction in SUA with increased uric acid deposits.[30] In present study, the adverse effects were joint pain in 26% and epigastralgia in 10%. The joint pains were not gouty arthritis. All patients were treated conservatively and none were excluded from study due to adverse effects.

Some of the limitations of this study is short duration, single center and no comparative group. However, based on our findings Febuxostat treatment seems effective in all pre-dialysis CKD patients with further multicenter, randomized controlled trial in CKD patients may answer some of the limitations of our study.

Conclusion

Our study found that Febuxostat therapy in hyperuricemic pre-dialysis CKD is beneficial with significant reduction of SUA in all stages

of CKD and improvement of eGFR in CKD stage 3 and 4 without significant adverse effects.

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Conflict of Interest
None

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None

Author Contribution
DS: Design of the study, acquisition of data, drafting and editing of manuscript to its final form. AB: Conception and design of study protocol and revision of manuscript. KD & JRS: Sample collection and editing of manuscript. RH: Design of study, statistical analysis, revising it critically and final approval of manuscript.

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