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ORIGINAL ARTICLE

Efficacy of Febuxostat for the Prevention of Progression of Chronic Kidney Disease in Hyperuricemia patients

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ABSTRACT

Background: Hyperuricemia has been linked with adverse outcomes in chronic kidney disease. Urate lowering drugs are recommended for treating hyperuricemia in CKD patients.
Aim: To determine efficacy of Febuxostat for the prevention of progression of chronic kidney disease in hyperuricemia patient.
Study design: Descriptive case series
Setting: Nephrology Department of Sheikh Zaid Hospital Lahore. Sample size 200 patients fulfilling the inclusion criteria were included. Serum urate and creatinine levels (to estimate eGFR) were assessed and patients were started on 40mg to 120mg once daily dose of febuxostat tablet, for a period of 12 weeks. The efficacy of the treatment was assessed after 12 weeks.
Result: Total 200 patients were included. The patient mean age was 36.2±9.251, mean eGFR was 36.3±11.79, mean serum urate levels were 8.65±1.134 and mean dose of febuxostat was 70.2±27.1. 71.5% were males and 28.5% females. Febuxostat was efficacious in 28.5% of the patients. The data was stratified by age, gender, febuxostat dose, and kidney disease severity. Post - stratification chi square test was1applied. It was seen that there was no significant relationship of efficacy with age. Gender and dose of febuxostat (P value of >0.05).
Conclusion: Febuxostat is effective in reducing the progression of chronic kidney disease in hyperuricemic patients.
Keywords: Hyperuricemia, Chronic Kidney Disease, Urate Lowering Drugs, Febuxostat

INTRODUCTION

Chronic1kidney disease (CKD) is thought to be a process that is irreversible[1]. It is considered that patients who have chronic kidney disease are1expected to experience a progressive deteriorating in the course of the disease.2 The rate of progression of the disease depends on the cause and it has been shown that different therapeutic strategies such as hypertension and proteinuria control can slow the progression[3].

In Chronic Kidney Disease, hyperuricemia has been linked to negative outcomes. Hyperuricemia is associated with macrovascular heart disease in patients with chronic kidney disease & in cross-sectional studies, there were high rates of decrease in glomerular filtration rate (GFR)[4,5].

It has been seen that 40-60% of patients with chronic kidney disease have hyperuricemia and also associated with its progression 1. There is no evidence regarding the cutoff value of serum levels of uric acid that are associated with the progression, however, it is clear that the risk of further kidney damage increases with an increase in concentration of uric acid[5,6,7].

In addition to lifestyle changes, medication with urate-lowering medicines is recommended for patients with hyperuricemia in chronic renal disease.4 Febuxostat is one such urate-lowering pharmaceutical medication. Febuxostat is a potent nonpurine selective inhibitor of Xanthine Oxidase & inhibits both the oxidized as well as decrease forms of the enzymes. It is an effective drug and is safe in patients who have hepatic and renal impairment of mild to moderate severity[8].

Febuxostat has previously been shown to be effective in slowing the progression of kidney damage in hyperuricemia patients in 34% of cases. 8 Another study showed that it was efficacious in 24.6% of the individuals in slowing the progression of kidney disease and decreasing uric acid levels[9].

A lot of international studies a has been carried out to assess the roles of this new agent in lowering the levels of serum urate and reducing the progression of renal insult. However, no such study has ever been conducted in Pakistan.

The rationale of the study was to evaluate the efficacy of febuxostat in slowing the progression of kidney disease and decrease uric acid levels in patients with hyperuricemia, so that awareness can be made among the treating physicians to treat this serious condition at an early stage with a drug that is safe and is efficacious to prevent further renal complications related to high serum urate levels and reduce further mortality and morbidity.

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METHODOLOGY

This Descriptive case series was conducted in 24th January, 2020 till 23rd July, 2020 the outpatient and the inpatient Department of Nephrology, Sheikh Zaid Hospital, Lahore after approval of Ethical Review Board of Sh. Zayed Hospital, Lahore. Sample size 200 was calculated by using WHO sample size calculator by taking 6% margin of error and 5% level of significance by taking expecting anticipated population proportion is 24.6%[9].

Patients with 20-50 years of age and who have hyperuricemia was labeled if the serum uric acid levels were ≥7.0mg/dl as determined by the blood samples taken from the patients and investigated and patients who have chronic kidney disease were included. Patients with history of hypertension (BP >160/90), hepatic impairment (AST, ALT >40 IU/L), patients on dialysis (eGFR <20 ml/min/1.73m2) or those who have undergone renal transplant and patients with a history of malignancy were excluded.

All of the patients gave their informed consent. All patients underwent a complete clinical examination as well as a detailed history of past treatment for hyperuricemia, dialysis & kidney transplant before treatment. Serum urate levels and serum creatinine levels (to estimate eGFR) were assessed by drawing an intravenous sample at baseline, and patients were started on 40mg to 120mg once daily dose of febuxostat tablet, for a period of 12 weeks. After 12 weeks, serum urate levels and serum creatinine levels were again assessed to see a decrease in the levels of serum uric acid and to see the effect on eGFR after treatment and efficacy was assessed of the drug.

SPSS was used to analyze the data. Age, eGFR value, Serum urate levels and dose of Febuxostat was calculated as mean & SD. Gender, efficacy of treatment & side effects was presented as frequency and percentages. Stratified data with respect to gender, age, febuxostat dose & kidney disease severity. The chi square test was used after stratification, and a P value < 0.05 was1considered as significant.

RESULTS

Total 200 patients were enrolled. The patients mean age was 36.2± 9.251 years. The mean eGFR, serum urate levels, dose of febuxostat of the patients was 36.3 ml/min/1.73±11.79 m2, 8.65±1.134, 70.2±27.1(Table 1).

There were 143(71.5%) males & 57(28.5%) females. Febuxostat was found to be efficacious in 37(28.5%) of the patients. The side effects seen were nausea in 55(27.5%), joint pains in 36(18%), rash in 20(10%), abnormal LFTs in 15(7.5%) and flaring up of gout in 20(10%) (Table 2).

The data was stratified by age, gender, febuxostat dose, and kidney disease severity. Post - stratification chi square test was1applied. It was seen that there was no significant relationship of efficacy with age. Gender and dose of febuxostat (P value of >0.05) (Table 3)

Table 1: Descriptives of Age eGFR, Gender etcc…..

		Frequency (%)
Age	Mean±_SD	36.2±9.251
eGFR	Mean±_SD	36.3±11.79
Serum Urate levels	Mean±SD	8.65±1.134
Dose of Feboxustat	Mean±SD	70.2±27.1
Gender	Male	143(71.5%)
	Female	57(28.5%)

Table 2: Distribution of efficacy and side effect

		Frequency (%)
Efficacy	**Yes**	60(30%)
	No	140(70%)
Side Effect	Nausea	55(27.5%)
	Joint Pains	36(18%)
	Rash	20(10%)
	Abnormal LFTS	15(7.5%)
	Gout Flare Up	20(10%)
	No Side Effects	54(27%)

Table 3: Association of age, gender and dose of febusostat with efficacy of drug

		Efficacy		**P value**
		Yes	**No**	
Age Groups	Young age (20-30 years)	24(12%)	38(19%)	0.12
	Early middle age (31-40 years)	6(8%)	50(25%)	
	Late middle age(41-50 years)	20(10%)	52(26%)	
Gender	Male	40 (20%)	103(51.5%)	0.543
	Female	20(10%)	37(18.5%)	
Dose of Febuxostat	Low Dose (40-80 mg)	25(12.5%)	72(36%)	0.253
	High Dose (120mg)	35(17.5%)	68(34%)	

DISCUSSION

Chronic kidney disease is associated with hyperuricemia, which is a common complication (CKD).10, 11 Furthermore, new evidence suggests that it is an independent risk factor for CKD. The kidneys regulate serum uric acid (SUA), that is the last result of purine metabolism in humans. Because excretion of uric acid in the urine is reduced in CKD patients, hyperuricemia is more common in this group of patients. According to previous research, every 1 mg/dL rise in uric acid increases the risk of hyperuricemia by 11%. Furthermore, people with hyperuricemia (>9 mg/dL) are three times more likely to develop CKD[12].

The present study showed that febuxostat was effective in 28.5% of patients with hyperuricemia in reducing the progression of1chronic kidney disease. It was not seen to be effected by age, gender, dose of febuxostat and severity of kidney disease. The study revealed that febuxostat was more efficacious at higher doses i.e. at 120mg compared to low doses 40mg and 80mg i.e. 16.5% vs 12% respectively.

Hyperuricemia is an independent risk factor for chronic renal disease.1 Injury to the kidney occurs as a result of huge increases or persistent elevation of serum uric acid.13 Based on the current study results and from obseravtions made previously, it has been noticed that the progression of chronic kidney disease significantly reduces if the levels of serum uric acid are decreased. In light of this, it is postulated that treatment with febuxostat may be efficacious in prevention of progression of deterioration of functions of kidneys in patients with chronic kidney disease[14].

Previous studies shows that having febuxostat can help to improve kidney tubulointerstitial tissue impairment and oxidative stress.15 Recent studies have found that febuxostat reduces serum uric acid levels, which has a renoprotective effect[16].

A meta-analysis published in 2018 assessed at the efficacy of1 febuxostat in patients with hyperuricemia moderate chronic renal disease. The results1showed that there was significant improvement in the estimated glomerular filtration rates of patients who had received febuxostat as a treatment for hyperuricemia in patients with1chronic kidney disease. Similar results have been produced by this current study[1].

In another single centered, febuxostat was compared with placebo to see its effect on the progress of decline of kidney functions in patients with stage 3 & 4 chronic kidney disease who had hyperuricemia but were asymptomatic. The study was carried out for six months. The authors estimated the frequency of patients who had >10% decline in the estimated rate of glomerular filtration between two groups. The results showed that 17(38%) people in the febuxostat group had an eGFR drop of more than 10% from baseline, compared to 26 (54%) in the placebo group (P0.004). The authors concluded that febuxostat slowed down deterioration of estimated glomerular filtration compared to placebo & thus had superior efficacy[9,17].

The efficacy of febuxostat in reducing renal function decrease in patients with hyperuricemia and chronic kidney disease was also shown in this study. The study had a few limitations, including a small sample size, a short follow-up period, and the fact that it was a single-center trial.

CONCLUSION

The conclusion of the study that estimated glomerular filtration is significantly improved in hyperuricemic patients with chronic kidney disease after receiving febuxostat. Furthermore, higher dose (120mg) had a superior efficacy over the other two lower doses i.e. 80mg and 40mg, and with the increase in the dose of medicine the effect was increased too. The data of this study suggests that febuxostat may be effective in reducing functional decline of kidneys by controlling the levels of serum uric acid.

Conflict of interest: Nil

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