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ORIGINAL ARTICLE

Effects of Febuxostat in the Progression of Chronic Kidney Disease in Renal Transplant Recipients

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ABSTRACT

Objective: To see the effect of febuxostat in slowing the progression that treatment with febuxostat improves eGFR in renal transplant recipients having asymptomatic hyperuricemia.

Patients and Methods: This randomized controlled trial was carried out in a Department of Nephrology PIMS. A total of 106 post renal transplants recipients having asymptomatic hyperuricemia, were randomly divided into two groups of 53 each by lottery method. One group was given febuxostat for treatment of post renal transplant hyperuricemia while the other one was given a placebo.

Results: The mean age of patients was 48.15 years with a male to female ratio 4.6:1. Treatment with febuxostat was linked significantly in lowering the mean uric acid level at 7.01mg/dl, 6.32mg/dl and 5.42mg/dl at 2, 4 and 6 months, respectively, and renal function was better preserved in the patients receiving febuxostat at mean eGFR of 49.74, 48.96 & 48.89 ml/min/1.73m ^{2} at 2, 4 and 6 months, respectively.

Conclusion: In patients with postrenal transplant asymptomatic hyperuricemia, febuxostat showed significant reduction in serum uric acid level with preservation of renal function.

Key words: Asymptomatic Hyperuricemia, eGFR, Febuxostat, Renal graft dysfunction, Renal transplant

Author`s Contribution
[1] Conception, synthesis, planning of research and manuscript writing Interpretation and discussion
[2,3] Data analysis, interpretation and manuscript writing, Active participation in data collection.

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Introduction

Uric acid is a weak Acid Trioxypurine, comprising of imidazole and pyrimidine substructure with molecules of oxygen. It is made from metabolic conversion of either endogenous or dietary purines mainly in intestines, muscles and liver [1]. Xanthine is the predecessor of uric acid which is metabolized into uric acid by the enzyme xanthine oxidoreductase i.e., xanthine-oxidase or xanthine dehydrogenase.[2] Uric acid is mainly excreted by kidneys approx. 250-750 mg/day, which is about 70% of daily urate production.[3] Post renal transplant hyperuricemia is defined as serum uric acid level >7.0mg/dl in men and >6.0mg/dl in women, having renal transplantation.[4] Identification of new risk factors help in improvement of long-term outcomes. Numerous factors predisposing renal transplant recipients to hyperuricemia were reported, including treatment with diuretics, insufficient allograft function and immunosuppression with cyclosporine.[5]

Asymptomatic hyperuricemia is a risk factor for cardiovascular disease and for the onset and progression of chronic kidney disease in general population.[6,7] Chung et al investigated whether early-onset hyperuricemia has clinical importance irrespective of graft function.[8] Post renal transplant hyperuricemia is linked with the onset of

cardiovascular disease and allograft loss in renal transplant recipients.[9,10] Numerous studies have been done in kidney transplant recipients to assess the role of hyperuricemia in decreased renal function, but there has been a controversy in the results. The commonly used hypouricemic agents used in general population are Allopurinol and Benzbromarone but both of them cannot be used in post renal transplant hyperuricemia because of toxicity of the former and reduced hypouricemic effect due to chronic renal insufficiency and renal transplantation in the latter.[11] Febuxostat is a non-purine selective inhibitor of xanthine oxidase and is better tolerated in patients with gout and/or moderate renal dysfunction.[12,13] Metabolism of Febuxostat is mainly done by glucuronide formation and oxidation in the liver.[14] However, the assessment of efficacy of febuxostat in kidney transplant recipients with asymptomatic hyperuricemia has not been done in local population so far.

Table 1: Baseline and Demographic Characteristics of Study Groups (n=106)

Characteristics	Group A Febuxostat (n=53)	Group B Placebo (n=53)	P value
Age (years)	48.38 ±8.61	47.92 ±8.70	0.788
<45 years	22 (41.5%)	23 (43.4%)	0.844
≥45 years	31 (58.5%)	30 (56.6%)	0.844
Gender			
Male	43 (81.1%)	44 (83.0%)	0.800
Female	10 (18.9%)	9 (17.0%)	0.800
Weight (Kg)	98.66 ±12.56	97.91 ±11.79	0.750
Serum creatinine (mg/dl)	1.84 ±0.27	1.85 ±0.35	0.912
eGFR using MDRD equation (ml/min/1.73m^2)	50.38 ±5.23	50.13 ±5.10	0.807
Serum Uric Acid (mg/dl)	8.83 ±0.71	8.80 ±0.70	0.812

**Chi-square test and independent sample t-test, observed difference was statistically insignificant*

Patients and Methods

It is a prospective randomized controlled trial conducted in Department of Nephrology, Pakistan Institute of Medical Sciences, Islamabad, Pakistan over 6 months i.e., from 18th September 2017 to 17th March, 2018. Sample size was calculated using WHO sample size calculator. In total 106 patients (87 males and 19 females), selected by non-probability, consecutive sampling, were enrolled, and after informed consent were divided into 2 groups of 53 each, using lottery method. All renal transplant recipients with age from 20-60 years in PIMS nephrology OPD or ward, 3 months' post-transplantation with asymptomatic hyperuricemia, males having serum uric acid of >7.0 mg/dl and females having serum uric acid level > 6mg/dl, eGFR > 35ml/min/1.73m ^{2}, patients with cyclosporine levels in therapeutic range and, no previous history of gout. Group A was given febuxostat with adjusted dose according to individual eGFR of the participant using MDRD study equation. Group B was given placebo. Determination of serum uric acid levels and eGFR was done in both the groups at 2, 4 and 6 months and then both serum uric acid levels and eGFR were compared in both the groups at 2, 4 and 6 months. Nephrotoxic drugs were avoided in this time period. Patients with malignancy, hypersensitivity to febuxostat, already on any of the following drugs; probenicid, benzbromarone, fenofibrate, diuretics or azathioprine, patients having ALT and AST more than twice the upper limit of laboratory reference range, pregnancy and patients non-compliant to protein diet.

Results

The mean age of the patients was 48.15±8.61 years, having 87 (82.1%) males and 19 (17.9%) female patients, with a male is to female ratio of 4.6:1. Demographic characteristic are presented in (Table 1). Treatment with febuxostat was linked with significant lowering of mean serum uric acid level at 2 months (7.01±0.35 mg/dl vs 8.69±0.74 mg/dl; p < 0.001), at 4 months (6.32 ±0.33 mg/dl vs 8.78 ± 0.78 mg/dl; p < 0.001) and at 6 months (5.42 ± 0.28 mg/dl vs 8.58 ± 0.72 mg/dl; p<0.001). It preserved renal function, which was evident from significantly higher mean eGFR with febuxostat at 2 months (49.74 ± 4.67 ml/min/1.73m^2 vs 47.34 ± 5.10 ml/min/1.73m^2; p<0.013), at 4 months (48.96 ± 4.88 ml/min/1.73m^2 vs 43.00 ±5.43 ml/min/1.73m^2; p < 0.001) and at 6 months (48.89 ± 4.72 ml/min/1.73m^2 vs 40.92 ± 4.99 ml/min/1.73m^2; p < 0.001) as compared with placebo (Table 2).

Table 2: Comparison of Various Laboratory Parameters between the Groups over 2, 4 and 6 Months Follow-up (n=106)						
Lab Parameter	**Characteristic**	**0**	**2 months**	**4 months**	**6 months**	**P value**
Serum creatinine(mg/dl)						
	Febuxostat	1.84±0.27	1.87±0.28	1.88±0.32	1.91±0.29	0.487
	Placebo	1.85±0.35	1.99±0.35	2.05±0.30	2.25±0.38	0.006*
	P value	0.912	0.070	0.005*	<0.001*	
eGFR (ml/min/1.73m^2)						
	Febuxostat	50.38±5.23	49.74±4.67	48.96±4.88	48.89±4.72	0.788
	Placebo	50.13±5.10	47.34±5.10	43.00±5.43	40.92±4.99	0.028*
	P value	0.807	0.013*	<0.001*	<0.001*	
Serum Uric Acid (mg/dl)						
	Febuxostat	8.83±0.71	7.01±0.35	6.32±0.33	5.42±0.28	<0.001*
	Placebo	8.80±0.70	8.69±0.74	8.78±0.78	8.58±0.72	0.207
	P value	0.812	<0.001*	<0.001*	<0.001*	

*Independent sample t-test, *observed difference was statistically significant*

Discussion

In order to improve long-term outcomes of kidney transplantation, new risk factors are required to be recognized that result in poor outcomes.[5] Post- transplant hyperuricemia occurs in renal transplant recipients.[4] Uric acid lowering drugs help to control serum uric acid levels and improve graft function.[14-17] However, the available evidence contains controversy. Moreover, there was no such local published data available that triggered the need for this study.

We observed that in patients on febuxostat, serum creatinine level gradually increased over 6 months but the difference was statistically insignificant. Our results are comparable to those of Tojimbara et al, who also reported similar insignificant difference in mean serum creatinine in renal transplant patients with asymptomatic hyperuricemia on febuxostat treatment over 3 to 6 months' interval from baseline.[14] Oh et al also reported similar insignificant rise in creatinine in such patients over 6 months.[16] eGFR decline in our study was also statistically insignificant. However, in present study, we found that treatment with febuxostat in post renal transplant recipients lead to significant reduction in serum uric acid level over 2, 4 and 6 months' follow-up from baseline, (8.83±0.71 mg/dl vs. 7.01 ±0.35 mg/dl vs. 6.32 ±0.33 mg/dl vs. 5.42 ±0.28 mg/dl; p<0.001). Our observations are in line with Tojimbara et al, who also observed similar decline in serum uric acid levels in patients with post renal transplant hyperuricemia recipients treated with febuxostat over 3 and 6 months (8.0 ±0.8 vs. 6.3 ±0.9 vs. 5.7 ±0.7 mg/dl).[14] Similar reduction in mean serum uric acid level has been reported by Sofue et al (8.4 0.3 vs. 6.2 0.3 vs. 6.4 0.3 vs 6.2 0.3 mg/dl; p<0.05) after 1, 3 and 6 months of treatment.[15]

Conclusion

The present study indicates that patients with asymptomatic hyperuricemia after 3 months of renal transplantation, febuxostat treatment was linked with significant decrease in serum uric acid level with preservation of renal function evident from insignificant difference in the mean eGFR. The present study is the first of its kind in local population and advocates the routine use of febuxostat in hyperuricemic post renal-transplant recipients. A very strong limitation to the present study was limited follow-up of 6 months. Consequently, long term results of febuxostat treatment on serum uric acid and kidney function were not considered. Studies involving long term follow-up are recommended in future research.

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