DOI: https://doi.org/10.53350/pjmhs2115113293

ORIGINAL ARTICLE

Change in Glomerular Filtration Rate with Febuxostat in Patients with Advanced Chronic Renal Failure

ISHTIAQ ALAM[1], FAHEEM USMAN SULEHRI[2], MUHAMMAD ABDUL AZIM BAIG[3], MAIRA BHATTI[4], FOUZIA PERVEEN[5], SABEEN ARJUMAND[6]

[1]*Senior Registrar Nephrology, Armed Forces Hospital, Southern Region, Khamis Mushayet, KSA*
[2]*Assistant Professor Nephrology, Central Park Teaching Hospital, Kahna Nau, Lahore*
[3]*Specialist Nephrology, Hamad General Hospital, Doha, Qatar.*
[4,5,6]*Assistant Professor,Pharmacology. Sharif Medical and Dental College,Lahore.*
Correpondence to: Ishtiaq Alam, Email: Ishtiaq182@yahoo.com, Cell: 0345-4138308

ABSTRACT

Background: Chronic kidney disease (CKD), is defined as progressive loss in kidney function. The study evaluated the mean change in estimated glomerular filtration rate (eGFR) with febuxostat in patients of advanced chronic kidney dysfunction with hyperuricemia.

Methodology: A prospective observational study was conducted at the department of Nephrology, Sheikh Zayed Hospital, Lahore for 6 months, from January 2019 to October 2019. At baselines, the blood sample was obtained and sent to the laboratory for assessment of serum creatinine level. The eGFR was calculated by using the MDRD formula. Patients were then advised to take one oral Febuxostat 40 mg daily for 6 months. After 6 months, the blood sample was obtained for assessment of serum creatinine level.

Results: The mean age of the patients was 40.72±14.90 years, male to female ratio was 1:1. The mean value of eGFR at baseline was 23.53±11.09 and its mean value at 6th month was 34.28+12.31, which was significant (p<0.001).

Conclusion: Febuxostat effectively improved estimated glomerular filtration rate (eGFR) in patients presenting with advanced chronic kidney dysfunction with hyperuricemia.

Keywords: Hyperuricemia, Kidney, Disease, Febuxostat, Dysfunction, Glomerular, Filtration

INTRODUCTION

Hyperuricemia is a new and potentially important mediator of renal disease. Increased levels of uric acid in the blood leads to hyperuricemia which increases the risk of being diagnosed with Gout.[1] Recent studies show that hyperuricemia has a major impact on progression to CKD (chronic kidney disease), hypertension, metabolic acidosis and heart failure which shows that hyperuricemia needs to be managed properly even if patients are asymptomatic. [2,3]

Hyperuricemia affects kidneys by preglomerular vasculopathy leading to ischemia in post glomerular circulation. It also causes Hypertension via activation of RAS and COX-2.[4] Furthermore, Hyperuricemia induces pro-inflammatory cytokines like Monocyte Chemoattractant Protein-1. The main issue in management of patients suffering from hyperuricemia is side effects due to drug usage which gets worse in patients who already have dysfunctional kidneys.[5]

Allopurinol is excreted by the kidneys in the form of oxypurinol which in turn can accumulate in the kidneys and lead to toxicity in patients who have dysfunctional kidneys. Moreover, drugs like Probencid are relatively contraindicated in CKD patients because of increased incidence of urolithiasis and low efficacy in kidney dysfunction.[6-7]

Febuxostat, a non purine Xanthine Oxidase inhibitor, is being used as a different approach for the managing hyperuricemia presenting with CKD since it will need lesser adjustment of the dose in association with kidney function.[8] In a study it was noticed that with febuxostat, the mean eGFR was decreased from 27.3±10.6ml/min/1.73m^2 to 26.0±10.4ml/min/1.73m^2, so the change of 1.3±0.2ml/min/1.73m^2 was observed from baseline and after 6 months of the treatment. [6]

But another study has reported that with febuxostat, the mean eGFR was increased from 31.5±13.6 to 33.7±16.6 (ml/min/1.73m) at 6 months, so the change of 2.2±3ml/min/1.73m^2 was observed from baseline and after 6 months of the treatment. [9] There is inconsistency in the current literature therefore, the present study was conducted to evaluate the efficacy of febuxostat in improving the glomerular filtration rate in patients with advanced chronic renal failure.

METHODOLOGY

A quasi experimental study was conducted at the Department of Nephrology at Sheikh Zayed Hospital in Lahore between January 2019 to October 2019. A sample size of 40 cases was calculated with 95% confidence level, d=1 and taking magnitude of change in eGFR i.e. 2.2±3ml/min/1.73m^2 with febuxostat in patients of advanced chronic kidney dysfunction with hyperuricemia.

Non-probability consecutive sampling technique was used to enroll participants. All patients who were older than 18 years regardless of their gender were included in the study. Patients who had hyperuricemia (uric acid level >8 mg/d) and with advanced CKD for ≥3 months (stage 3-5). Patients who had ALT (>40IU) or AST (>40IU), a medical record of concurrent or recent (within 2 weeks) gouty attack or of AKI or Dialysis dependence were excluded from the study. Patients with a history of hypersensitivity to febuxostat and who were currently using Azathioprine or Mercaptopurine were not included in the study. Pregnant or breastfeeding women or those women who are anticipating pregnancy were also excluded from the study. Only 40 Patients satisfying the inclusion criteria were included in the study from OPD of Department of Nephrology, Sheikh Zayed Hospital, Lahore. Informed written consent was

taken from each patient prior to inclusion in the study. Relevant demographic details (name, age, weight, stage of CKD and duration) were noted. At baselines, the blood sample was obtained by using a 5cc BD syringe through aseptic measures and was shifted in vials containing ringer's solution. All samples were sent to the laboratory of the hospital for assessment of serum creatinine level. Reports were assessed and with the help of serum creatinine level, eGFR was calculated by using MDRD formula.

Then patients were advised to take one oral Febuxostat 40 mg daily. Then patients were followed-up in OPD till the end of 6 months. After 6 months, the blood sample was obtained by using a 5cc BD syringe through aseptic measures and was shifted in vials containing ringer's solution. All samples were sent to the laboratory of the hospital for assessment of serum creatinine level. Reports were assessed and with the help of serum creatinine level, eGFR was calculated by using MDRD formula (as per operational definition) and change in eGFR (increase or decrease) was noted (as per operational definition). Follow up was ensured by taking telephone contact.

All data was analyzed in SPSS version 21.0. Mean and standard deviation was calculated for variables like age and eGFR (baseline and end of trial) and change in GFR. The paired sample t-test was used to compare the pre and post treatment results with p value≤0.05 as significant. Frequency and percentage was calculated for gender and CKD stage. The change in eGFR was calculated by subtracting baseline eGFR and eGFR at the end of study. Data was stratified for age, gender, duration of CKD and stage of CKD. Post-stratification, paired sample t-test was applied taking p-value≤0.05 taken as significant.

RESULTS

Table 1. Baseline Characteristics of Study Population

Characteristics	n= 40
Age (years)	40.73 ± 14.9
Weight (Kg)	69.53 ± 5.88
Duration of disease (months)	14.05 ± 1.55
eGFR (at baseline)	23.53 ± 11.09
eGFR (at 6 months)	34.28 ± 12.31
change in eGFR	10.75 ± 3.4
Gender	
Female	20 (50%)
Male	20 (50%)
CKD Stage	
3rd	11 (27.5%)
4th	16 (40%)
5th	13 (32.5%)

The mean age of the patient was 40.73 ± 14.9 years and mean weight was 69.53 ± 5.88 kg. The mean baseline GFR and final GFR were 23.53 ± 11.09 and 34.28 ± 12.31, respectively. The change in eGFR is 10.75 ± 3.4 (Table 1).

The study reported a significant improvement in the glomerular filtration rate after six months of treatment with febuxostat (p<0.0001) (Table 2).

Table 2. Change in eGFR at Six months of Febuxostat Treatment

eGFR	e-GFR	p-value
At baseline	23.53 ± 11.09	<0.0001
At 6 months	34.28 ± 12.31	

Upon stratifying the data according to sociodemographic and clinical profile, it was found that the more advanced the disease was, the lesser the improvement in the GFR was observed (p<0.0001). Male gender had significantly greater improvement in the GFR as compared to females (p<0.0001) (Table 3).

Table 3. Stratification of eGFR according to the Demographic variables

	e-GFR		
	At baseline	At 6 months	p-value
Age (years)			<0.0001
≤ 35	21.08 ± 11.25	31.93 ± 13.17	
> 35	24.56 ± 11.09	35.68 ± 11.81	
Gender			<0.0001
Male	24.7 ± 11.16	35.2 ± 12.62	
Female	22.35 ± 11.18	33.35 ± 12.24	
CKD stage			<0.0001
3rd	38.18 ± 6.1	49.55 ± 5.15	
4th	22.75 ± 4.55	35.06 ± 5.47	
5th	12.08 ± 1.71	20.38 ± 3.04	

DISCUSSION

This study was conducted in the Nephrology Department of Sheikh Zayed Hospital in Lahore to determine the mean change in glomerular filtration rate (GFR) with febuxostat in individuals of advanced CKD with hyperuricemia. Febuxostat, a non-purine Xanthine Oxidase inhibitor, is being studied as a good alternate management option for hyperuricemia in patients presenting with CKD.[10]

According to our study results by the use of febuxostat the mean eGFR at baseline was 23.53±11.09 and at 6th month was 34.28 ± 12.31. By applying paired t-tests, a highly significant difference was found between the eGFR at baseline and at 6th month values i.e. p-value<0.0001. Hiroyuki Matsushima and Atsushi Oyam conducted a study which concluded that usage of febuxostat in low dosages can ultimately be safe and

effective in CKD patients who present with mild to moderate cases of hyperuricemia. [11]

Another study by Sakai Y et al. showed that uric acid mean level was reduced from 8.4 to 6.2 in 6 months and around 47.5% of individuals were able to achieve a uric acid level of less than 6 mg/dl. Febuxostat therefore decreases uric acid levels and stops the kidney from going into renal failure.[12]

Another study by Mayuko Ishikawa et al. described in their study that the mean value of eGFR at baseline of the CKD patients was 20.1±10.5 and its mean value at 2nd month was 20.7±10.2. They concluded that the Febuxostat is more efficacious in CKD patients with a high baseline serum UA concentration. Febuxostat caused no withdrawal symptoms and had no adverse effects.[13]

In a study it was noticed that with febuxostat, the mean eGFR was decreased from 27.3 ± 10.6ml/min/1.73m^2 to 26.0±10.4ml/min/1.73m^2, so the change of 1.3±0.2ml/min/1.73m2 was observed from baseline and after 6 months of the treatment.[14] Kimura et al., revealed that there was no significant difference observed in eGFR between febuxostat and the control group. Patients without proteinuria and those with lower serum creatinine benefitted more with febuxostat. [15] On the other hand, one study showed that the GFR in patients who were given febuxostat had no significant increase. Patients in the febuxostat group, 17 of 45 (38%) patients were found to have a ≥ 10% reduction in GFR above the baseline as compared to 26 of 48 (54%) patients in the placebo group.[16]

The impact of hypouricemic drugs for the maintenance of kidney function in CKD patients with advanced disease needs to be checked for long term usage of febuxostat.

CONCLUSION

According to our study results it has been proved that the febuxostat is efficacious and reliable drug and showed significant change in baseline and 6th month values of estimated glomerular filtration rate (eGFR) in patients presenting with advanced chronic kidney dysfunction with hyperuricemia.

REFERENCES

1. Oh TR, Choi HS, Kim CS, Bae EH, Ma SK, Sung SA, Kim YS, Oh KH, Ahn C, Kim SW. Hyperuricemia has increased the risk of progression of chronic kidney disease: propensity score matching analysis from the KNOW-CKD study. Scientific reports. 2019 Apr 30;9(1):1-9.
2. Kang DH, Nakagawa T. Uric acid and chronic renal disease: possible implication of hyperuricemia on progression of renal disease. InSeminars in nephrology 2005 Jan 1 (Vol. 25, No. 1, pp. 43-49). WB Saunders.
3. Avram Z, Krishnan E. Hyperuricaemia—where nephrology meets rheumatology. Rheumatology. 2008 Jul 1;47(7):960-4.
4. Ohno I. Relationship between hyperuricemia and chronic kidney disease. Nucleosides, Nucleotides and Nucleic Acids. 2011;30(12):1039-44.
5. Keenan RT, O'Brien WR, Lee KH, Crittenden DB, Fisher MC, Goldfarb DS, et al. Prevalence of contraindications and prescription of pharmacologic therapies for gout. The American journal of medicine. 2011;124(2):155-63.
6. Shibagaki Y, Ohno I, Hosoya T, Kimura K. Safety, efficacy and renal effect of febuxostat in patients with moderate-to-severe kidney dysfunction. Hypertension Research. 2014;37(10):919-25 .
7. Curiel RV, Guzman NJ, editors. Challenges associated with the management of gouty arthritis in patients with chronic kidney disease: a systematic review. Seminars in arthritis and rheumatism; 2012: Elsevier.
8. Sezai A, Soma M, Nakata KI, Osaka S, Ishii Y, Yaoita H, Hata H, Shiono M. Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients with chronic kidney disease (NU-FLASH trial for CKD). Journal of cardiology. 2015 Oct 1;66(4):298-303.
9. Juge PA, Truchetet ME, Pillebout E, Ottaviani S, Vigneau C, Loustau C, Cornec D, Pascart T, Snanoudj R, Bailly F, Cornec-Le Gall E. Efficacy and safety of febuxostat in 73 gouty patients with stage 4/5 chronic kidney disease: A retrospective study of 10 centers. Joint Bone Spine. 2017 Oct 1;84(5):595-8.
10. Lim DH, Oh JS, Ahn SM, Hong S, Kim YG, Lee CK, Choi SW, Yoo B. Febuxostat in hyperuricemic patients with advanced CKD. American Journal of Kidney Diseases. 2016 Nov 1;68(5):819-21.
11. Matsushima H, Oyama A. FP256EFFICACY AND SAFETY OF LOW-DOSE TREATMENT OF FEBUXOSTAT IN MILD-TO MODERATE CHRONIC KIDNEY DISEASE (CKD) PATIENTS WITH HYPERURICEMIA. Nephrology Dialysis Transplantation. 2015;30(suppl 3):iii152-iii
12. Sakai Y, Otsuka T, Ohno D, Murasawa T, Sato N, Tsuruoka S. Febuxostat for treating allopurinol-resistant hyperuricemia in patients with chronic kidney disease. Renal failure. 2014;36(2):225-31.
13. Akimoto T, Morishita Y, Ito C, Iimura O, Tsunematsu S, Watanabe Y, et al. Febuxostat for hyperuricemia in patients with advanced chronic kidney disease. DTI 2014;8:39.
14. Tsuruta Y, Mochizuki T, Moriyama T, Itabashi M, Takei T, Tsuchiya K, Nitta K. Switching from allopurinol to febuxostat for the treatment of hyperuricemia and renal function in patients with chronic kidney disease. Clinical rheumatology. 2014 Nov 1;33(11):1643-8.
15. Kimura K, Hosoya T, Uchida S, Inaba M, Makino H, Maruyama S, Ito S, Yamamoto T, Tomino Y, Ohno I, Shibagaki Y. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. American Journal of Kidney Diseases. 2018 Dec 1;72(6):798-810.
16. Sircar D, Chatterjee S, Waikhom R, Golay V, Raychaudhury A, Chatterjee S, et al. Efficacy of febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: a 6-month, double-blind, randomized, placebo-controlled trial. American journal of kidney diseases. 2015;66(6):945-50.