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Febuxostat Reduces Arterial Stiffness in Patients with Chronic Kidney Disease

Syed Mujtaba Hussain Naqvi,
Shobha Jagdish Chandra and T. Ramesh Kumar R.

Department of Clinical Pharmacology and Therapeutics,
Nizams Institute of Medical Sciences, Hyderabad AP, India

Abstract: Increased arterial stiffness is a hallmark of chronic kidney disease and is associated with adverse alterations in cardiac structure and function that may predispose to an increased risk of cardiovascular death. Hyperuricemia injure endothelial function and represents a risk factor for arterial stiffness. The present study attempts to assess the role of febuxostat on arterial stiffness in patients with chronic kidney disease. Placebo-controlled, randomized, double-blind, parallel-group study for 12 weeks. The study included patients with chronic kidney disease and hyperuricemia. The eligible patients received either febuxostat 40 mg once daily or placebo in 2:1 randomization for 12 weeks. The primary outcome measure was change in augmentation index compared to baseline in two groups. Secondary outcome measure included change in augmentation pressure, sub endocardial viability ratio and serum uric acid levels measured at baseline and at the end of study.The data on baseline and efficacy parameters for arterial stiffness was represented as mean ± SD. Paired Student t-test was used to compare the difference within the group, at 80% power and $P<0.05$.There was 6.92% mean reduction of AIx in febuxostat compared to 3% increase in placebo arm, $P<0.05$. There was also a significant reduction in AP and uric acid and improvement in SEVR compared to baseline and placebo in febuxostat group. There was no significant change in safety laboratory parameters during study. In this study Febuxostat reduced arterial stiffness which is cardiovascular risk factors in chronic kidney disease patients.

Key words: Febuxostat · Arterial Stiffness · Chronic Kidney Disease

INTRODUCTION

Many clinical and epidemiological studies have documented that patients with impaired kidney function are at increased risk of CV events and mortality [1]. Notably, the association of CKD and CV events is significant even with mild decrements of renal function not sufficiently severe to result in elevated serum creatinine [2]. Clinical studies have shown that damage of large conduit arteries is a major contributing factor for the high incidence of congestive heart failure (CHF), LVH, ischemic heart disease (IHD), sudden death, cerebrovascular accidents and peripheral artery diseases. Damage to large conduit arteries is principally related to highly calcified occlusive atherosclerotic lesions and to stiffening of large capacitive arteries. These two complications are independent risk factors for survival and improvement of arterial stiffness is associated with better prognosis and survival [3] Although traditional CV risk factors identify subjects at risk for cardiovascular disease (CVD), they do not accurately predict survival in CKD patients and the arterial stiffness is a significant and independent predictor of microvascular damage as well as CV outcome.

Large central arteries play a key role in converting the pulsatile cardiac outflow into a continuous blood flow throughout the arterial tree. In systole, the heart pushes a volume of blood (equal to stroke volume) into the thoracic aorta (Ejection phase). Because fluids are uncompressible, the stroke volume distends the thoracic aorta. By stretching, the arterial wall accumulates the elastic energy that maintains the blood flow during diastole when the ejection phase is over (Windkessel effect). Thus, the pulsatile flow is converted into a

Corresponding Author: Syed Mujtaba Hussain Naqvi, Department of clinical pharmacology and therapeutics, Nizams Institute of Medical sciences, Hyderabad AP,22-3-382/2 Mandi Mir Alam, Hyderabad AP, Tel: +08712729572, Facsimile :08978308919.

continuous flow by the cyclic distention and recoiling of central arteries. CV risk factors leads to arterial wall remodeling and reduced arterial compliance which negatively affect the process that converts the pulsatile in continuous blood flow impairing the oxygen supply to peripheral tissues. Thus, arterial stiffness might be considered as a measure of arterial damage due to the cumulative exposure of aging and different traditional and non-traditional CV risk factors [4].

A seminal paper by Wang and coworkers [5] showed a clinically meaningful increase in the aortic pulse wave velocity (PWV), an accurate and reproducible parameter of arterial stiffness, with estimated glomerular filtration rate (eGFR) decline which suggest that arterial stiffness increases with progressive worsening of renal function.

Hyperuricemia may injure endothelial function via resistin-dependent mechanisms and increases arterial stiffness [6] Serum uric acid (sUA) is considered to be an independent risk factor for both cardiovascular disease and CKD. Elevated sUA predicts the development of hypertension, obesity, diabetes and CKD. Importantly, emerging clinical data show that lowering sUA has both cardiovascular and renal benefits [7].

Treatments that reduce cardiovascular events in non-CKD patients do not always do so in CKD; for example, statins alone do not always reduce cardiovascular events in severe CKD. [8-10] This implies that one cannot necessarily extrapolate clinical trial results from non-CKD patients to CKD patients and that highly novel approaches might be required to reduce cardiovascular events in CKD patients.

Increased UA levels may be an indicator of up-regulated activity of xanthine oxidase, a powerful oxygen radical-generating system in human physiology. Increased reactive oxygen species (ROS) accumulation contributes to endothelial dysfunction, metabolic and functional impairment, inflammatory activation and other features of cardiovascular pathophysiology. Accordingly, inhibition of xanthine oxidase activity has been shown to improve a range of surrogate markers in patients with CVD [11]. In CKD patients, allopurinol, a xanthine oxidase inhibitor has found to regress left ventricular mass and improve endothelial/vascular function among patients with CKD. [12] Febuxostat, a novel, orally administered, non–purine analogue inhibitor of xanthine oxidase was more effective than allopurinol in lowering serum uric acid levels [13]. The main aim of the present pilot study was to assess if febuxostat lowers arterial stiffness in patients with chronic kidney disease.

MATERIALS AND METHODS

Study Population: Twenty four male and female adult subjects who were diagnosed with CKD (GFR<60 ml/min per 1.73 m^2) and hyperuricemia with above the normal institutional reference values (>7.0 in males, >6.1 in females) and arterial stiffness with AIx more than that of normal reference age were recruited from the Nephrology department for the study during the period of June 2011 to December 2011. Patients were excluded if any of the following criteria were present: already on allopurinol, febuxostat or other urate lowering agent, active gout, patients on dialysis, known patient with coronary artery disease or other cardiovascular disorders, severe hepatic disease, metastatic malignancy or other life-threatening diseases, pregnant or lactating women and unable to give informed consent.

Study Design: This was a 12 weeks, placebo-controlled, randomized, double-blind, parallel-group study. After baseline assessments and investigations, patients were then randomly assigned to receive a febuxostat 40 mg tablet once daily or a placebo capsule once daily for 12 weeks. Baseline blood samples were taken for renal function, liver function, TSH levels and ureate levels and these were repeated at the end of the study. Discontinuation criteria were intolerance to treatment and the participant voluntary withdrawal from the study.

During the trial study, patients were allowed to continue all of their concomitant treatment. All patients provided written informed consent and the Nizam's Institute Ethics Committee (NIEC) approved the study. Investigators allocating the treatment according to randomization schedule generated by computer in 2:1 fashion were different from investigator who analyzed the efficacy outcome by measuring arterial stiffness to ensure blindness.

Applanation Tonometry: A full clinical history of the eligible patients was taken including measurements of height and weight. Subjects were rested in a supine position for at least 10 min after which blood pressure was measured in triplicate using an automated blood pressure monitor (Omron705 CPII). Applanation tonometry was performed using Sphygomo Cor (AtCor, Australia) over the right radial artery, with the subject in the supine position, for pulse wave analysis (PWA) to calculate Augmentation index (AIx). All readings recorded met the manufacturer's quality control standards integrated into

the software package. Augmentation pressure (AP), sub endocardial viability ratio (SEVR) was also recorded using the same procedure. The applanation tonometry was performed at two visits (baseline and 12 weeks) using the Sphygmocor system. A single trained investigator who was blind to the allocated treatment performed the PWA.

The safety laboratory parameters were recorded at baseline and at the end of the study.

RESULTS

A total of 20 patients who met the criteria were included for the study and 18 (febuxostat, n = 12; placebo, n = 6) completed the study. There were no significant differences between both groups with respect to demographic or baseline characteristics, apart from the serum bilirubin which were still in normal range. GFR, uric acid level, AIx were also similar at baseline (Table 1). Two patients withdrew during the course of the study one in febuxostat group due to personal reason unrelated to study drug and one in the placebo group due to progression of disease. There was significant reduction in augmentation index (AIx), on treatment with febuxostat (Table 2 and Figure 1) which had increased in the placebo at the end of 12 weeks. There was also a significant decrease in augmentation pressure and improvement in sub endocardial viability ratio with febuxostat at 12 weeks (Table 3 and Figures 2, 3) but there was no significant change in these parameters in placebo group. The correlation between percentage change in serum uric acid with the percentage change in augmentation index was mild but statistically non significant (r=-0.2, *p* 0.57), but the correlation between percentage change in augmentation pressure (r=-0.58, *p* 0.05) and subendocardial viability ratio (r=-0.62, *p* 0.04) with the percentage change in serum uric acid during 12 weeks was statistically significant. There was no significant change in aortic systolic and diastolic blood pressure, hepatic enzymes, blood urea, serum creatinine and TSH levels during the study. There were no serious adverse events or no patient had withdrawn due to adverse effects.

DISCUSSION

This is the first study to demonstrate that febuxostat can lower arterial stiffness in humans without primarily acting by reducing BP. Arterial stiffening is linked to decreased glomerular filtration rate and is predictive of kidney disease progression and the patient's

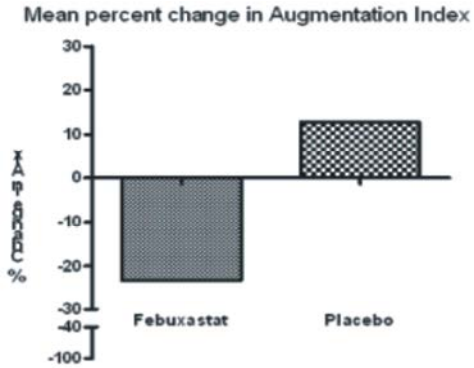

Fig. 1: Mean % change in augmentation index in febuxostat and placebo group. There was significant decrease in Aix in febuxostat group by 23.19% (p=0.03) whereas Aix increased in placebo group by

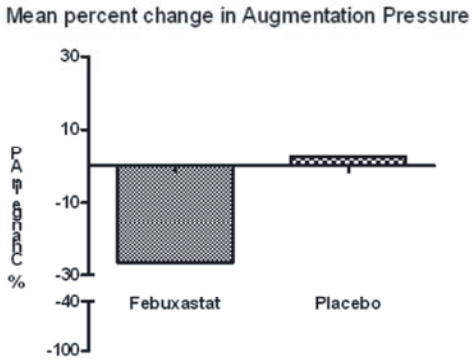

Fig. 2: Mean % change in augmentation pressure in febuxostat and placebo group. There was significant decrease in AP in febuxostat group by 26.56% (p=0.05) whereas AP increased in placebo group by 2.67%

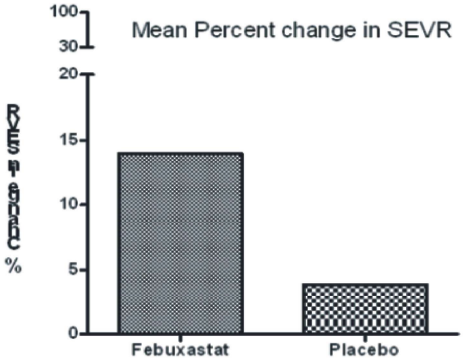

Fig. 3: Mean % change in Subendocardial viability ratio (SEVR) in febuxostat and placebo group. There was significant increase in SEVR in febuxostat group by 13.94% (p=0.05) whereas SEVR increased marginally in placebo group by 2.88% (P=0.63)

Table 1: Comparison of baseline characteristics of the two groups.

	Febuxostat Characteristics 40 mg (n=12)	Placebo (n=6)	p
Age (years)	46.5±10.38	49.33±10.15	0.99
Body surface area, g/m^2	24.54±3.61	28.7±8.58	0.19
Blood pressure, mmHg			
SBP	144.75±11.60	146.66±14.66	0.81
DBP	85.16±6.80	79±12.76	0.25
Creatinine clearance ml/min (Cockcroft method)	29.93±13.32	34.6±9.88	0.58
Uric acid (mg/dl)	8.99±1.88	6.9±0.52	0.08
SGOT (U/L)	19.83±5.79	23.66±9.87	0.38
SGPT (U/L)	21.5±2.93	21±9.41	0.86
Serum bilirubin (mg/dl)	0.61±0.22	0.26±0.11	0.02
TSH (IU)	1.92±1.50	1.53±1.61	0.69
AIx (%)	29.83±13.16	23.66±3.78	0.44
AP (mmHg)	16±13.65	12.33±7.09	0.66
SEVR (%)	120.08±14.04	120±22	0.99

Table 2: The change in various efficacy parameters in both the groups at the end of study

	Febuxostat group (n=12)				Placebo group (n=6)			
Parameter	Baseline	End of study	% change	p	Baseline	End of study	% change	p
Augmentation Index, AIx	29.83±13.16	22.91±14.65	-23.19%*	0.03	23.66±3.78	26.66±7.63	+12.67%#	0.37
Augmentation pressure, AP	16±13.65	11.75±11.75	-26.56%*	0.05	12.33±7.09	12.66±2.51	+2.67%#	0.94
Sub endocardial viability ratio (SEVR)	120.08±14.04	136.83±30.65	+13.94%*	0.05	120±22	124.66±35.24	+3.88%#	0.63
Uric acid (mg/dl)	8.99±1.88	5.71±1.42	-36.48%*	0.01	5.9±0.52	5.63±1.15	-4.57%#	0.67
Creatinine Clearance (ml/min)	29.93±13.32	36.07±22.42	+20.51%#	0.11	34.6±9.88	27.4±12.45	-20.8%#	0.31

Table 3: Comparison of AIx, AP and SEVR in patients with creatinine clearance <30 ml/min and >30 ml/min.

Parameter	Cclr<30	Cclr 31-60	p
Augmentation Index, AIx	36±13.56	21.2±6.37	0.04
Augmentation pressure, AP	22.28±14.91	7.2±3.63	0.05
SEVR	124±7.3	114.6±19.95	0.27

cardiovascular outcome. Premature vascular aging and arterial stiffening are observed with progression of chronic kidney disease (CKD). [15] In the present study we observed that the augmentation index and augmentation pressure which are indices of arterial stiffness were significantly higher in patients with creatinine clearance less than 30 ml/min compared to those with creatinine clearance between 30 to 60 ml/min, showing increased arterial stiffness with worsening creatinine clearance. (Table 5).

Aix, is a ratio calculated from the blood pressure waveform as augmentation pressure divided by pulse pressure. It depends on arterial wall stiffness but also on the amount of reflected energy which is determined by peripheral vascular resistance and is affected by heart rate variation. Thus, AIx is a combined measure of arterial stiffness and wave reflection. AIX is frequently and simplistically considered to be an index of arterial stiffness. AIX depends on many factors, including age, Pulse Wave Velocity, travelling distance of pressure waves (body height), Left Ventricular Ejection Time and reflective properties of the arterial system. Gérard *et al* predicted the risk ratio for each 10% increase in augmentation index was 1.51 for all-cause mortality and 1.48 for CV mortality in renal failure patients.[16] In our study there was 23.19% decrease in augmentation index with febuxostat 40 mg for 12 weeks, whereas the placebo group showed 12.67% increase in AIx when compared to baseline, which seems to be encouraging in preventing CV events in patients with CKD. Catherine *et al.* showed that Augmentation Pressure and Sub endocardial viability ratio were each univariately associated with microalbuminuria and glomerular filtration rate. A comparison between those with moderately to severely impaired renal function (eGFR<60) and those with normal to mildly impaired renal function (eGFR=60) showed a significant difference in AIx (p=.02) and AP (p=.006), but not SEVR (p=.13). Francesco F *et al.* concluded that AIx, an important measurement of arterial compliance, increases with age till about 55 years and slows down to a plateau thereafter. However, augmentation pressure continues to increase steadily with age, suggesting that AP should be measured in the elderly and not AI. In women, the value of this measurement of arterial stiffness is always higher than that in men, which is in part due to their lower height and a closer physical

proximity between the heart and the reflecting sites. AP should therefore be reported instead of AI when assessing the effect of age, gender and other factors on augmentation. [17] In our study there is 26.56% decrease in augmentation pressure which also reflects the decrease in arterial stiffness.

Each standard deviation decrease in SEVR was associated with a 56% increased risk for low eGFR (<60) (p=.02), was selected over brachial SBP and DBP measures and remained significantly associated with low eGFR after adjusting for heart rate and ACEI/ARB medication use. In our study SEVR improved by 13.94% and the corresponding percentage increase in creatinine clearance was 20.51%, although the increase in creatinine clearance was not statistically significant (p=0.11) [18]

Suyan *et al*. Serum UA levels are associated with alterations in systemic arterial stiffness [19]. As discussed above xanthine oxidase is a powerful oxygen radical-generating system in human physiology and the reduction of oxidative stress could probably explain the benefit of these group of drugs in reducing arterial stiffness. In our study the statistically significant correlation was observed between percentage changes in serum uric acid levels with the percentage change in augmentation index and augmentation pressure, indices of arterial stiffness. In this study febuxostat reduced arterial stiffness which is a cardiovascular risk factor in chronic kidney disease patients. However these findings need to be confirmed in large randomized controlled clinical trial.

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