EFFICACY AND SAFETY OF ORAL FEBUXOSTAT IN SUBJECTS WITH MODERATE-TO-SEVERE CHRONIC KIDNEY DISEASE (CKD): ONE-YEAR RESULTS

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INTRODUCTION: Hyperuricemia is currently considered an independent cardiovascular risk factor and an important mediator in renal disease development and progression. Febuxostat, a novel non-purine selective xanthine oxidase inhibitor, is more effective than allopurinol and equally safe in the management of chronic hyperuricemia. However, insufficient safety and efficacy data are available for Febuxostat administration to subjects with hyperuricemia and impaired renal function.

AIM OF THE STUDY: This study was designed to prospectively evaluate efficacy and safety of oral Febuxostat in hyperuricemic subjects with chronic kidney disease (CKD) stages 3-4.

PATIENTS AND METHODS:

- Nineteen patients, male/female 12/7, age 70 (41-86) years with serum uric acid (sUA) ≥ 8.0 mg/dl and serum creatinine (sCr) ≥ 2.0 mg/dl received Febuxostat for one year.
- Nine out of 19 patients were previously on allopurinol and, due to intolerance, hypersensitivity or lack of efficacy, were switched to Febuxostat after a 15-day washout period.
- Patients with renal transplantation, active liver disease, alcohol abuse, concomitant treatment with azathioprine, mercaptopurine, theophylline or severe, life threatening medical condition were excluded.
- Febuxostat starting dose was 80 mg orally every other day with creatinine clearance estimated by Cockcroft-Gault formula (eCrCl C-G) ≥ 30 ml/min and 80 mg every third day with < 30 ml/min. This dose was adjusted to achieve target sUA levels of < 6 mg/dl.
- Hematology and biochemistry blood tests and creatinine clearance with 24-hr urine collection (24hr-CrCl) were performed and eCrCl C-G as well as eGFR $MDRD_4$ were calculated at baseline and monthly thereafter. Adverse events were recorded.

Table: Patients characteristics

Number of patients	**19**
Male/female	**12/7**
Age (median, range) years	**70 (41-86)**
Serum uric acid at baseline (mg/dl)	**9.90±1.59**
Serum creatinine at baseline (mg/dl)	**2.60±1.06**
24hr-CrCl at baseline (ml/min)	**28.10±9.45**
eCrCl C-G at baseline (ml/min)	**28.60±9.54**
eGFR at baseline (ml/min/1.73m²)	**26.20±8.04**
Primary renal disease:	
Diabetic nephropathy	**4**
Chronic glomerulonephritis	**2**
Interstitial nephropathy-Nephrolithiasis	**1**
Scleroderma	**1**
Unknown nephropathy	**11**

RESULTS:

- sUA was significantly reduced already by month 1 of the study (5.6±1.5 vs. 9.9±1.6 mg/dl at baseline, p<0.001). This significant difference remained throughout the study period with stable and within target sUA levels up to month 12 (5.4±0.8 mg/dl, p<0.001). Target sUA at the end of the study was achieved in 16/19 (84.21%) patients.
- Renal function, assessed by sCr, 24hr-CrCl and eGFR C-G remained unchanged through month 12 vs. baseline (2.4±1.2 vs. 2.6±1.0 mg/dl, 29.80±10.37 vs. 28.10±9.45 ml/min and 31.80±11.90 vs. 28.60±9.54 ml/min, respectively), whereas eGFR $MDRD_4$ was found significantly higher by the end of follow-up period (29.84±10.69 vs. 26.16±8.04 ml/min/1.73m² at baseline, p=0.03).
- No significant differences were observed for the rest of the studied parameters, including C-reactive protein (CRP), proteinuria and liver tests.
- Febuxostat weekly dose variation was similar throughout the study in all patients.
- No significant differences were observed in the Febuxostat sUA lowering effect or in renal function evolution during treatment between males and females, diabetics and non-diabetics as well as CKD 3 and 4 patients.
- Gastrointestinal adverse events in 2/19 patients were mild.

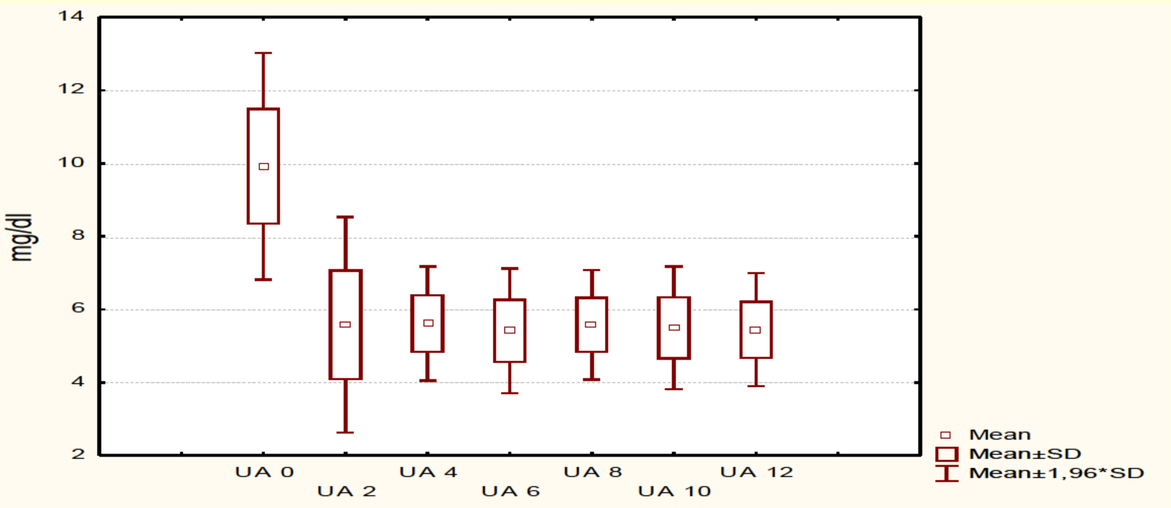
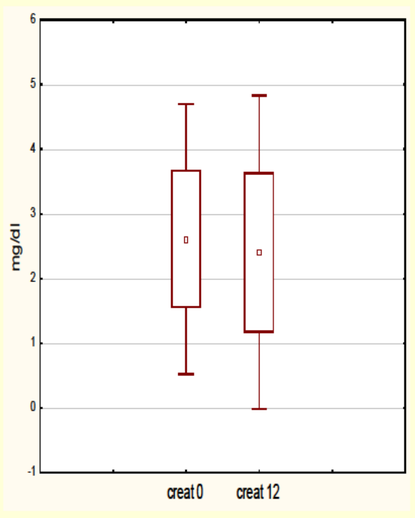


Fig 1: Serum uric acid at baseline and through month 12 of the study



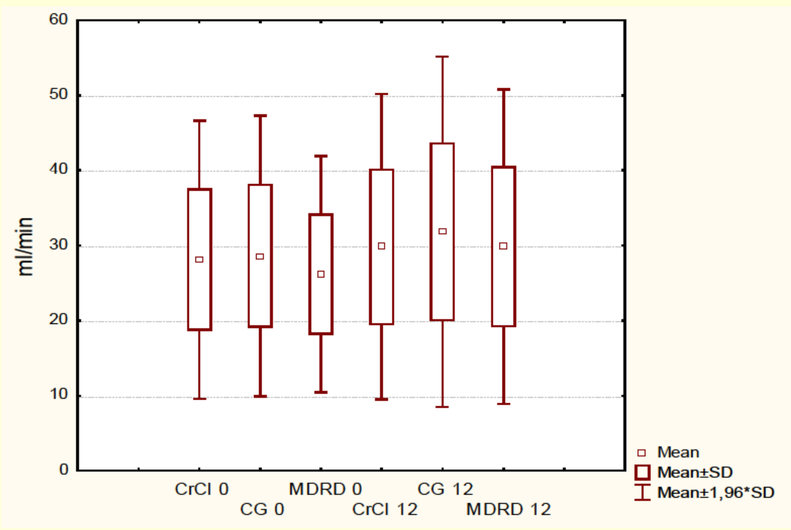


Fig 2: Renal function at baseline and at the end of the study

CONCLUSIONS:

Febuxostat, administered over one-year period in significantly reduced dosage, appears to be effective and safe with minimal side effects in the management of chronic hyperuricemia for patients with moderate-to-severe CKD. Larger studies with longer follow-up might conclusively determine potential beneficial impact of treatment with Febuxostat on renal function.

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