LONG-TERM EFFICACY AND SAFETY OF ORAL FEBUXOSTAT IN SUBJECTS WITH MODERATE-TO-SEVERE CHRONIC KIDNEY DISEASE: TWO-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, in particular over the long term.

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

PATIENTS AND METHODS:

- Fifteen patients, male/female 10/5, 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 two years.
- Nine out of 15 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 every other month thereafter. Adverse events were recorded.

Table: Patients characteristics

Number of patients	**15**
Male/female	**10/5**
Age (median, range) years	**70 (41-86)**
Serum uric acid at baseline (mg/dl)	**9.91±1.68**
Serum creatinine at baseline (mg/dl)	**2.56±0.74**
24hr-CrCl at baseline (ml/min)	**26.88±10.27**
eCrCl C-G at baseline (ml/min)	**28.53±9.64**
eGFR $MDRD_4$ at baseline (ml/min/1.73m²)	**25.80±7.54**
Primary renal disease:	
Diabetic nephropathy	**3**
Chronic glomerulonephritis	**2**
Interstitial nephropathy-Nephrolithiasis	**1**
Scleroderma	**1**
Unknown nephropathy	**8**

RESULTS:

- sUA was significantly reduced already by month 2 of the study (9.9±1.6 vs. 5.7±1.3 mg/dl, p<0.001). This significant difference remained throughout the study period with stable and within target sUA levels up to month 24 (5.3±0.7mg/dl, p<0.001). Target sUA at the end of the study was achieved in 12/15 (80%) patients.
- Renal function, assessed by sCr, 24hr-CrCl, eCrCl C-G and eGFR $MDRD_4$ remained unchanged through month 24 vs. baseline (2.56±0.74 vs. 3.12±2.09 mg/dl, 26.88±10.27 vs. 24.90±10.29 ml/min, 28.53±9.64 vs. 25.94±8.25 ml/min and 25.80±7.54 vs. 24.20±9.32 ml/min/1.73m², respectively).
- 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 2/15 (13.3%) patients were mild.

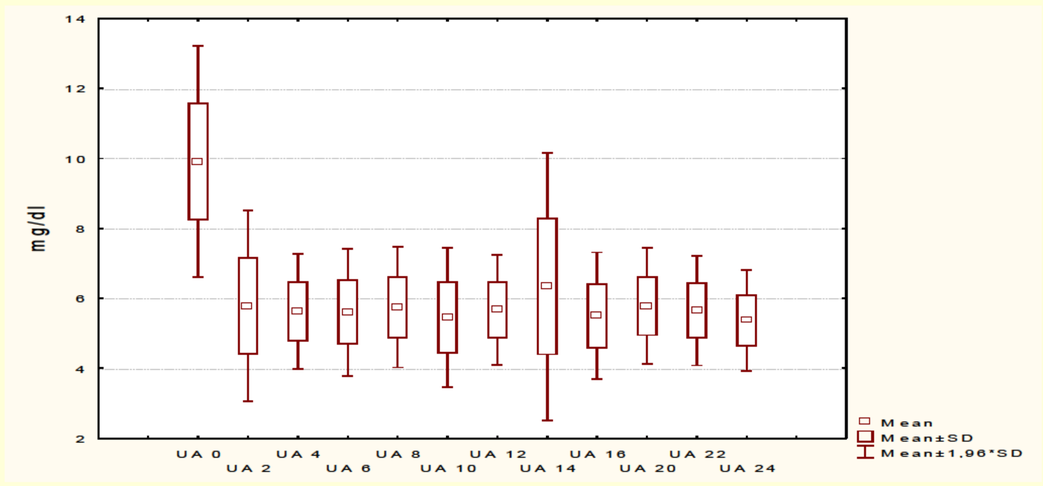
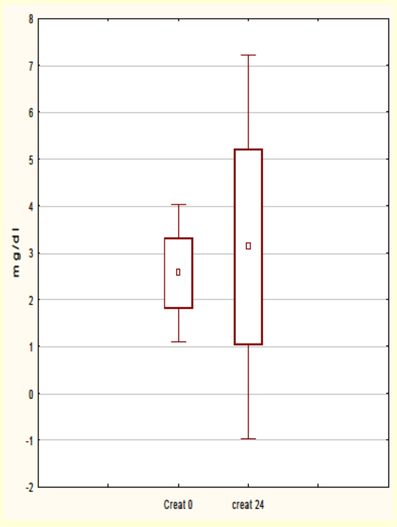


Fig 1: Serum uric acid at baseline and through month 24 of the study



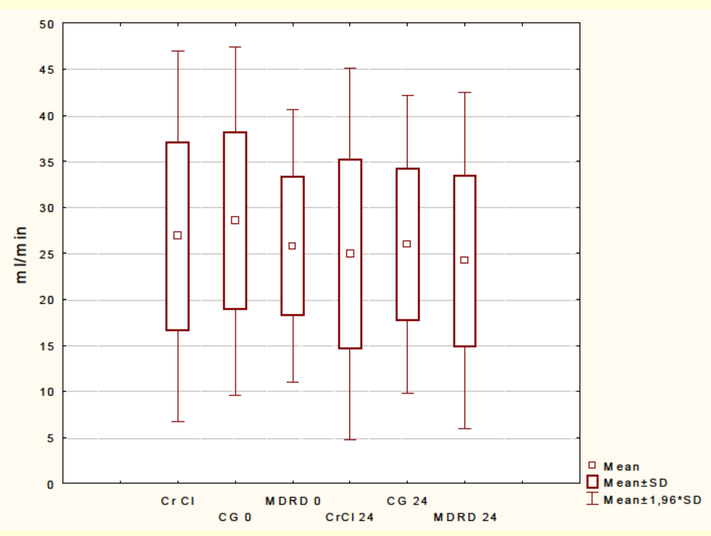


Fig 2: Renal function at baseline and at the end of the study

CONCLUSIONS:

Febuxostat, administered over a two-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.

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