EFFICACY AND SAFETY OF ORAL FEBUXOSTAT COMPARED TO ALLOPURINOL IN SUBJECTS WITH MODERATE-TO-SEVERE CHRONIC KIDNEY DISEASE

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INTRODUCTION: Hyperuricemia is highly prevalent in patients with chronic kidney disease (CKD) and may contribute to renal disease development and progression. Therefore, uric acid-lowering therapy appears beneficial. Allopurinol has been associated with increased risk of toxicity in patients with CKD. Febuxostat, a novel non-purine selective xanthine oxidase inhibitor, is an alternative to allopurinol in the management of chronic hyperuricemia. However, insufficient safety and efficacy data are available for Febuxostat administration to subjects with impaired renal function.

AIM OF THE STUDY: This study evaluated efficacy and safety of oral Febuxostat compared to allopurinol in hyperuricemic subjects with stages 3-4 CKD.

PATIENTS AND METHODS:

- Thirty-eight patients received Febuxostat for one year with a Febuxostat starting dose of 80 mg orally every other day with creatinine clearance estimated by Cockcroft-Gault formula (eCrCl C-G) ≥ 30 ml/min and every third day with < 30 ml/min. This dose was adjusted to achieve target sUA levels of ≤ 6 mg/dl.
- A well-matched group of 17 patients received allopurinol for one year with an Allopurinol starting dose of 100 mg daily that increased gradually up to 300 mg.
- Patient baseline characteristics for both groups are reported in Table 1.
- Patients with renal transplantation, active liver disease, alcohol abuse, concomitant treatment with azathioprine, mercaptopurine, theophylline or severe, life threatening medical condition were excluded in both groups.
- Hematology, biochemistry blood tests and creatinine clearance with 24-hr urine collection (24hr-CrCl) were performed. eCrCl C-G as well as eGFR $MDRD_4$ were calculated at baseline and every other month thereafter. Adverse events were recorded.

Table 1: Patient baseline characteristics

	Febuxostat Group	Allopurinol Group
Number of patients	38	17
Male/female	24/14	10/7
Age (median, range, years)	70 (41-86)	72 (35-86)
Serum uric acid (mg/dl)	9.9±1.5	8.9±0.8
Serum creatinine (mg/dl)	2.4±0.8	2.2±0.6
24hr-CrCl (ml/min)	31.3±13.1	35.6±5.1
eCrCl C-G (ml/min)	31.9±12.7	33.2±5.3
eGFR $MDRD_4$ (ml/min/1.73m^2)	29.1±10.7	33.2±4.7
Primary renal disease:		
Diabetic nephropathy	11	7
Chronic glomerulonephritis	4	2
Polycystic kidney disease	0	1
Interstitial nephropathy-Lithiasis	1	0
Scleroderma	1	0
Unknown nephropathy	21	7

Results:

- Baseline characteristics were similar in both groups, with the exception of sUA that was significantly higher in Febuxostat group (9.9±1.5 vs. 8.8±0.8 mg/dl, p=0.009).
- An equivalent reduction in sUA levels was found in both groups already by month 2 of the study (5.9±1.3 in Febuxostat vs. 6.1±1.1 mg/dl in Allopurinol group) and was maintained throughout the study period with stable and within target sUA levels up to month 12 (5.4±0.6 vs. 5.7±0.6 mg/dl).
- Target sUA at month 12 was achieved in 33/38 (86.8%) patients in Febuxostat group and 15/17 (88.2%) in Allopurinol group.
- Renal function, assessed by sCr, 24hr-CrCl, eGFR C-G and eGFR $MDRD_4$, remained stable or improved in both groups, significantly higher at month 12 only in eGFR C-G (p=0.02) of the Febuxostat group and in 24hr-CrCl (p=0.02), eGFR C-G (p=0.04) and eGFR $MDRD_4$ (p=0.01) of the Allopurinol group).
- 24hr-CrCl at month 12 was higher in Allopurinol group (p=0.01), with a trend, although non-significant, towards better sCr, eGFR C-G and $MDRD_4$, as well.
- No significant differences were observed for the rest of the studied parameters, including C-reactive protein (CRP), proteinuria and liver tests both between and within groups.
- Mild gastrointestinal adverse events were recorded in 5/38 (13.1%) patients of the Febuxostat group, whereas none was reported in Allopurinol group.

Table 2: Serum uric acid throughout the study

Serum Uric Acid (mg/dl)	Febuxostat Group	Allopurinol Group
sUA 0	9.9 1.5	8.8 0.8
sUA 2	5.9 1.3	6.1 1.1
sUA 4	5.6 0.7	5.9 1.0
sUA 6	5.6 0.8	5.8 0.7
sUA 8	5.5 0.7	5.4 1.1
sUA 10	5.4 0.7	5.7 0.6
sUA 12	5.4 0.6	5.7 0.6

Table 3: Renal function at baseline and at the end of the study

	Febuxostat Group	Allopurinol Group
sCr 0 (mg/dl)	2.4 0.8	2,2 0.6
sCr 12 (mg/dl)	2.2 1.0	2,1 1.2
24hr-CrCl 0 (ml/min)	31.3±13.1	35.6±5.1*
24hr-CrCl 12 (ml/min)	33.3±16.0	44.7±13.6*
eCrCl C-G 0 (ml/min)	31.9±12.7*	33.2±5.3*
eCrCl C-G 12 (ml/min)	34.8±14.8*	37.7±8.9*
eGFR $MDRD_4$ 0 (ml/min/1.73m^2)	29.1±10.7	33.2±4.7*
eGFR $MDRD_4$ 12 (ml/min/1.73m^2)	31.6±13.0	38.4±8.8*

*Significant changes in 0 vs. 12 month values

CONCLUSIONS:

Febuxostat, administered over one-year period appears to be comparable to allopurinol in terms of uric acid-lowering effect and safety with minimal side effects in the management of chronic hyperuricemia for patients with moderate-to-severe CKD. Renal function improved in both groups, significantly in most parameters of the Allopurinol group and less consistently in the Febuxostat group.

REFERENCES:

1. Filiopoulos V, Hadjiyannakos D, Vlassopoulos D. New insights into uric acid effects on the progression and prognosis of chronic kidney disease. Ren Fail 2012; 34: 510-520
2. Schumacher HR, Becker MA, Wortmann RL, Macdonald PA, Hunt B, Streit J, Lademacher C, Joseph-Ridge N. Effects of Febuxostat Versus Allopurinol and Placebo in Reducing Serum Urate in Subjects With Hyperuricemia and Gout: A 28-Week, Phase III, Randomized, Double-Blind, Parallel-Group Trial. (APEX). Arthritis & Rheumatism 2008; 59: 1540-1548
3. Becker MA, Schumacher HR, Espinoza LR, Wells AF, MacDonald PA, Lloyd E, Lademacher C. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. Arthritis Research & Therapy 2010; 12: R63

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