To evaluate the uric acid lowering efficacy of Febuxostat in patients with chronic renal failure stage III

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Abstract:
The present study was done to evaluate the uric acid lowering efficacy of Febuxostat in patients with chronic renal failure stage III. A single centered open label study was conducted in 30 patients for 4 weeks. Tablet Febuxostat 40 mg once daily resulted in significant serum uric acid reductions. Liver function and estimated glomerular filtration rate (eGFR) were not significantly altered. Febuxostat is safe potent hypouricemic drug in patients with moderate renal impairment.

Keyword: Hyperuricemia, chronic renal failure, febuxostat, eGFR

INTRODUCTION:
Renal diseases are on the rise with increasing life span and increase in non communicable diseases. The past decade has seen progress in the treatment of chronic kidney disease (CKD). The identification of novel risk factors and new treatments for CKD remains a major goal of medical research. And some old risk factors are reemerging. One such risk factor is uric acid. Uric acid is identified as a new and potentially important mediator of renal disease progression. Apart from kidney disease, there is increasing evidence that uric acid may cause hypertension and metabolic syndrome. Once uric acid enters a cell, it can cause oxidative stress and activate the local rennin angiotensin system. Hyperuricemia also induces vascular disease via cyclo oxygenase-2 dependent pathway. Hyperuricemia is common in patients with CKD. There are only few studies to show that lowering uric acid slows renal disease progression. One uncontrolled study has suggested that withdrawal of chronic allopurinol therapy may result in worsening hypertension and accelerated loss of renal function. A controlled clinical trial of allopurinol in 54 patients with hyperuricemia and mild to moderate chronic kidney disease resulted in decreased progression of disease at 12 months of therapy. And lowering of uric acid was found to slow the renal disease progression with febuxostat. The study with febuxostat was done in 5/6 nephrectomy rats. The present short clinical trail with
Febuxostat was done in patients with CKD and hyperuricemia to evaluate the uric acid lowering efficacy. For the past 30 years, allopurinol, has been the mainstay of chronic treatment in patients with hyperuricemia. 20% of patients using allopurinol reports adverse events and 5% discontinue its use. The mortality due to allopurinol hypersensitivity syndrome may reach 25%. Particularly, people with kidney failure or having concomitant thiazide diuretic therapy are the vulnerable group. Also, allopurinol requires dose reduction in renal impairment, this being its route of excretion. The inadequacies of allopurinol, in terms of limited efficacy at the usual dose of 300mg/day, need for dose adjustment in patients with renal impairment, undesirable side effects, tissue damage by toxic or immunological mechanisms have highlighted the need for additional treatment for hyperuricemia. Febuxostat is structurally different from allopurinol and lacks the purine ring. It is a more selective and potent inhibitor of xanthine oxidase than allopurinol and has no effect on other enzymes involved in purine or pyrimidine metabolism. The onset of action of febuxostat is sufficiently fast that serum uric acid levels can be re-tested within 2 weeks of initial dosing. Febuxostat is well absorbed after oral administration (84% oral bioavailability). The effects of food or antacids on absorption are not considered to be clinically relevant and febuxostat can be given without regard to food intake. The half-life is 5–8 hours, and the volume of distribution at steady state ranges from 29 to 75 liters after an oral dose of 10–300 mg. Febuxostat is almost completely bound to plasma proteins (99% binding), primarily albumin. The active metabolites of febuxostat are 82–91% protein bound. Studies show that Febuxostat 10-120mg daily behaves linearly. It is metabolized and excreted by the liver, so no dose adjustment is necessary in patients with mild-to-moderate renal impairment or mild-to-moderate hepatic impairment. Febuxostat has to be started a 40 mg daily and it can be titrated up to 80 mg. Forty mg of febuxostat was superior to allopurinol 300 mg (in mild renal impairment) or 200 mg (in moderate renal impairment).

**AIM OF THE STUDY**

The present study evaluates the efficacy of Febuxostat in reducing serum uric acid levels in patients with moderate renal impairment and hyperuricemia.

**STUDY DESIGN AND PROCEDURES**

This prospective, open label, phase 4 study was conducted in a single centre, Nephrology outpatient department at Government Rajaji Hospital, Madurai. Institutional ethical committee approval was obtained. Written informed consent was obtained from all the patients in language understandable by the patients. Baseline serum uric acid was defined as the value obtained at the time of enrollment.

**INCLUSION CRITERIA**

1. Adult patients of both sexes, age 18 years.
2. Chronic renal failure stage III i.e. estimated GFR by Cock Craft Gault formula 30-59 ml/min.
3. Hyperuricemia defined as serum uric acid >6.6 mg/dl in men and >6mg/dl in women.
EXCLUSION CRITERIA
1 Secondary hyperuricemia due to malignancy, tumour lysis syndrome, organ transplant recipients.

2 Patients already on other urate lowering drugs such as allopurinol.

3 Acute gout

4 Laboratory findings: Severe renal impairment – creatinine clearance < 30 ml/min, active liver disease.

5. Concomitant medication: Azathioprine, thiazides, aspirin>325mg/day, other salicylates, angiotensin receptor blockers, statins. (Losartan and statins were found to increase the uric acid levels.17,18)

6 Nursing and pregnant women.

7 Women of child bearing age group not following any acceptable contraceptive procedures.

METHODOLOGY:
About 200 out patients attending the nephrology outpatient department was screened. 30 patients were fit for the study. eGFR (estimated glomerular filtration rate) was obtained using the Cockcroft Gault formula. eGFR=(140-age) (weight in kg)/72(serum creatinine mg/dl). For females, this value has to be multiplied by 0.85 eGFR values of 30 to 59 ml/min indicates stage 3 renal failure.19 Detailed history was obtained from all the patients enrolled and recorded in the proforma designed. Basic investigations like hemoglobin, serum electrolytes, fasting blood sugar, urine routine, liver function tests were done. Subjects received 40mg febuxostat daily for 2 weeks. Patients were instructed to take the tablets daily in the morning after food. Patients were seen at the end of first, second, third and fourth weeks. Compliance was checked during the first two visits by asking them and also by verifying the empty strips. Patients were instructed to report any adverse effect by contacting the investigator through phone whenever necessary or to come to the outpatient department or reporting during their weekly visits. Assessment at the end of first week included a detailed history, physical examination, recording vital signs and assessment of adverse events. At the end of second week, complete physical examination, assessment of adverse events and the laboratory investigations which includes serum uric acid, serum creatinine, liver function tests were done. In this study, the patient themselves acted as controls. Parameters such as serum uric acid, eGFR and liver function tests taken at the time of enrollment served as control. The same were evaluated at the end of 2 weeks. Follow up was done at the end of fourth week and serum uric acid levels were repeated.'

STUDY END POINTS
Efficacy analyses were carried out on all subjects who received 40 mg day febuxostat for at least 2 weeks. The primary efficacy end point was the proportion of subjects who achieved serum uric acid levels of <6mgdl. The secondary end point was the percentage reduction from baseline serum uric acid. Safety was analyzed by assessing adverse events, by comparing eGFR and liver function tests before study and at the end of 2 weeks.
RESULTS:
BASE LINE CHARACTERISTICS
Serum uric acid levels were obtained before and after taking the drug for 2 weeks. Statistical analysis was done using student's paired t test.

Among the 30 subjects, 80% were male (24/30). Mean age of the subjects was 48.4 years. Mean body weight was 53.3 kg. Mean serum uric acid level at the time of enrollment was 9.73 mg/dl. 26.6% had serum uric acid levels 10 mg%.
Most common comorbid conditions were hypertension 83.3% (25/30), hyperlipidemias 26.6% (8/30), diabetes 20% (6/30), coronary artery disease 6% (2/30) and retinopathy 3% (1/30). During study, almost all patients were on other drugs, commonly anti hypertensives, anti dyslipedemics, hypoglycemic agents and 36.6% (11/30) were on frusemide.

EFFICACY:
Treatment with tablet Febuxostat resulted in significant reduction in serum uric acid levels (p value < 0.01). 43.3% (13/30) of all subjects had serum uric acid levels < 6 mg% at the end of 2 weeks. Achieving this primary end point was maximum when initial uric acid levels were 9-10 mg%. Mean percentage reduction of uric acid was 47.3%.

SAFETY AND ADVERSE EFFECTS:
E G F R and liver enzymes were not significantly affected (p value > .05). Adverse effects were seen in 2 patients. The adverse effects were cough (1/30) and epigastric pain (1/30). They were mild and self limiting; needed no treatment or dose reduction or drug withdrawal. They were reported to the ethical committee and was permitted to continue the study.

FOLLOW UP:
Serum uric acid levels at the end of four weeks were found to be in the pre treatment levels.

DISCUSSION:
Hyperuricemia is common in patients with renal disease, but it is never considered as risk factor for progression. Two studies found that hyperuricemia is an independent risk factor for progression of IgA nephropathy. Another recent study found that increasing serum uric acid levels were positively associated with CKD. This association appeared to be independent of age, gender, smoking status, alcohol intake, education, diabetes mellitus, hypertension, body mass index and total cholesterol levels. Febuxostat is an orally administered nonpurine selective inhibitor of xanthine oxidase (XO).
Febuxostat is a potent ligand for, and inhibitor of, both the oxidized and reduced forms of XO.
Clinical studies have also shown that febuxostat produces significant dose-dependent decreases in serum uric acid levels. In addition, febuxostat has minimal effects on other enzymes of purine and pyrimidine metabolism. Febuxostat is primarily metabolized by hepatobiliary conjugation. Also, febuxostat was found to reduce serum uric acid levels in majority of subjects within 7 days of therapy. Limitations verify the trends described. Long term efficacy of febuxostat in lowering the cardiovascular mortality & reno protective effect has to be studied.

CONCLUSION:
In the present study with 30 patients, majority were in the age group of 45 to 65 years of age. About 46% had serum uric acid levels of 9 to 10 mg%. Two weeks treatment of
Febuxostat resulted in prompt and statistically significant reduction of serum uric acid levels. Patients’ compliance was good. There were minimal adverse effects. And there were no statistically significant changes in eGFR and in liver function tests. If supported by future prospective studies, uric acid-lowering medication may be an effective strategy to prevent and/or arrest chronic kidney disease.
Figure 3. eGFR before and after study

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