



CHRONIC GOUT AND HYPERURICEMIA; TREATMENT WITH FEBUXOSTAT VERSUS ALLOPURINOL

Dr. Faaiz Ali Shah¹, Dr. Haziqdad Khan², Dr. Kifayatullah³, Dr. Ismatullah⁴, Dr. Zulfiqar Ali Durrani⁵,
Dr. Zahir Khan⁶

1. MBBS, FCPS (Orthopaedics),
Senior Registrar
Department of Orthopaedics & Trauma,
Mardan Medical Complex
Teaching Hospital,
Bacha Khan Medical College Mardan KPK
2. MBBS, FCPS (Orthopaedics),
Assistant Professor
Department of Orthopaedics & Trauma,
Mardan Medical Complex Teaching Hospital
3. MBBS, FCPS (Orthopaedics),
Associate Professor
Department of Orthopaedics & Trauma,
Mardan Medical Complex Teaching Hospital
4. MBBS, FCPS (Orthopaedics),
Professor
Department of Orthopaedics & Trauma,
Mardan Medical Complex Teaching Hospital
5. MBBS, MS (Orthopaedics),
District Trauma Surgeon
Department of Orthopaedics & Trauma
6. MBBS, FCPS (Orthopaedics),
Medical Officer
Department of Orthopaedics & Trauma,
Mardan Medical Complex Teaching Hospital

Correspondence Address:

Dr. Faaiz Ali Shah
MBBS, FCPS (Orthopaedics)
Senior Registrar Department of
Orthopaedics & Trauma
Mardan Medical Complex Teaching Hospital
Bacha Khan Medical College Mardan KPK
faaizalishah@yahoo.com

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ABSTRACT... Objective: To assess the urate-lowering efficacy and safety of Febuxostat versus Allopurinol in subjects with hyperuricemia and gout. **Study design:** Randomized controlled trial. **Place and duration of study:** Department of Orthopaedic and Trauma Surgery Mardan Medical Complex Teaching Hospital Bacha Khan Medical College Mardan from February 2012 to March 2013. **Material and Methods:** Fifty patients of chronic gout and hyperuricemia fulfilling the inclusion criteria were divided into two equal groups by random method having 25 patients each and received either a fixed dose (80 mg) of Febuxostat (Group A) or Allopurinol (Group B) 300mg once daily for 16 weeks. The primary end point was the percentage of patients reaching serum urate level <6.0 mg/dl (360 μ mol per liter) at final visit. The secondary end points include reduction in the incidence of gout flares and adverse drug reactions. **Results:** There were 16(64%) males and 9(36%) females with mean age 44.92 years in group A while group B had 15(60%) males and 10(40%) females with mean age 46.24 years. At final visit Febuxostat group had mean uric acid level of 4.72 mg/dl \pm 1.56 SD while Allopurinol group had mean serum uric acid level of 6.34 mg/dl \pm 1.82 SD with majority of patients (84%, n=21) in group A achieving serum uric acid level of < 6 mg/dl (360 μ mol/l) while only 60 percent (n=15) of the patients in group B had serum urate level of < 6 mg/dl. (P = <0.05). Gout flare was reported in 12% (n=3) of group A patients and 36% (n=9) in group B patients. Adverse drug reactions were reported in 12% (n=3) of group A patients while 24% (n=6) in group B. **Conclusions:** Febuxostat lowered serum uric acid levels more potently than Allopurinol while having minimal gout flares and side effects.

Key words: Gout, Hyperuricemia, Febuxostat, Allopurinol.

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INTRODUCTION

Gout is the most common form of inflammatory arthritis in men, affecting 1-2% of adult men in Western countries¹ and an increasing number of postmenopausal women². The clinical manifestations of gout (acute gouty arthritis, gouty arthropathy, chronic tophaceous gout, uric acid urolithiasis, and gouty nephropathy) result from deposition of monosodium urate or uric acid crystals from supersaturated body fluids³. A target level for serum uric acid of < 6 mg/dl (360 μ mol/l) is recommended in evidence-based recommendations from the European League against Rheumatism (EULAR)⁴. The British Society

for Rheumatology (BSR) has also published guidelines for gout which recommend a lower serum uric acid target level of 5 mg/dl (300 μ mol/l)⁵. The drugs available for the treatment of hyperuricemia in patients with gout are uricosuric agents (e.g. probenecid, sulfinpyrazone), which increase the excretion of uric acid, and xanthine oxidase inhibitor (e.g. allopurinol and its metabolite oxypurinol), which inhibit the oxidation of xanthine to uric acid⁶. For many years, Allopurinol has been the most widely used urate-lowering agent in gout patients. The inadequacies of Allopurinol, in terms of limited efficacy at the usual dose of 300 mg, need for dose adjustment in

patients with renal impairment and undesirable side-effects, have highlighted the need for an additional treatment for patients with gout. The emergence of Febuxostat as a well-tolerated and efficacious gout therapy could prove to be an excellent solution⁷. Febuxostat acts as a potent inhibitor of xanthine oxidase and was found to be more than 10- 30 times potent than Allopurinol in animal studies⁸. The k_i value of Febuxostat is 0.7 nM as compared to Allopurinol which is 0.7 μ M. It has minimal effects on other enzymes involved in purine and pyrimidine metabolism⁹. No dose adjustment is required for mild to moderate renal failure but caution is required for severe impairment¹⁰. In this study, we assessed and compared the efficacy of Febuxostat and Allopurinol in reducing serum uric acid concentrations in patients with hyperuricemia (=8.0 mg/dl) and gout.

MATERIAL AND METHODS

A total of 50 patients with chronic gout and hyperuricemia were recruited from Out Patient Department (OPD) of Orthopaedic Surgery Unit Mardan Medical Complex Teaching Hospital Bacha Khan Medical College Mardan. Patients of both sex and all ages with a diagnosis of gout according to the American College of Rheumatology preliminary criteria¹¹ and a consensus panel of experts from the European League Against Rheumatism (EULAR)⁴ with serum urate level \geq 8.0 mg/dl and with normal renal function were included in the study. Females who were nursing or pregnant were not enrolled. All patients with active liver disease, or hepatic dysfunction, or steroid therapy (within 1 month of study) or hormone replacement/oral contraceptive therapy (within 3 months of study) were excluded from the study. Subjects already receiving urate-lowering therapy underwent a two-week washout period before undergoing randomization. Institutional review board approval was obtained, and all subjects provided written informed consent. Irrespective of their age and gender these 50 patients were randomly assigned to either group A (Febuxostat 80 mg once daily - Zurig, Getz Pharma®) or group B (Allopurinol 300 mg once daily- Xyloric, GlaxoSmithKline®) having

25 patients each for 16 weeks. Prophylaxis against gout flare with Naproxen 250 mg twice daily was provided to all patients in both groups during week 1 through 4. Follow-up visits occurred every 4th week through week 16. At each visit all patients underwent physical examination, vital signs were recorded, the serum urate concentration was measured, gout flares, and adverse drug reactions were recorded. The primary end point was the proportion of subjects in each treatment group with serum urate level $<$ 6.0 mg/dl (360 μ mol per liter)² at final visit. The secondary end points include reduction in the incidence of gout flares and adverse drug reactions. The collected data was transferred and analyzed using SPSS Version 15. Mean and standard deviation was calculated for quantitative variables like age and serum uric acid level. Frequency and percentage was calculated for qualitative variables like gender. T test was used to compare serum uric acid level with $P=0.05$ was taken statistically significant.

RESULTS

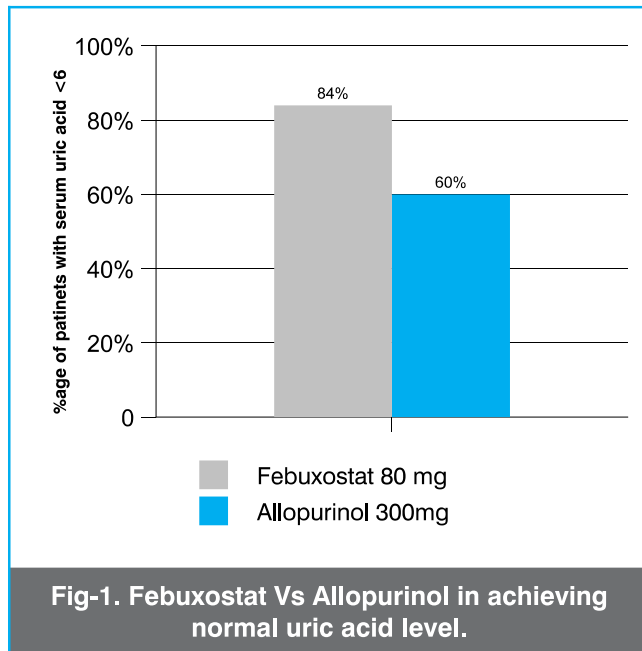
Fifty patients were randomly assigned to either group A (Febuxostat 80 mg once daily) or group B (Allopurinol 300 mg once daily) having 25 patients each for 16 weeks. Mean age of patients in group A was 44.9 ± 9.49 SD and mode 45 years, group B had mean age 46.2 years ± 10.42 SD with median 45 years. The mean age of all the patients in both groups was 45.5 years. Distribution of patients according to the gender is shown in Table No. I

Gender	Group A (n=25)		Group B (n=25)	
	Frequency	%age	Frequency	%age
Male	16	64	15	60
Female	9	36	10	40

Table-I. Distribution of patients according to the gender

Eighty percent (n=20) of the patients in group A while 84% (n=21) of the patients in group B were already receiving urate-lowering therapy and underwent a two-week washout period before undergoing randomization. Base line mean serum

uric acid of group A was 9.6 mg per deciliter while group B had 9.8 mg per deciliter. At final visit Febuxostat group had mean uric acid level of 4.72 mg/dl \pm 1.56 SD while Allopurinol group had mean serum uric acid level of 6.34 mg/dl \pm 1.82 SD with majority of patients (84%, n=21) in group A achieving serum uric acid level of < 6 mg/dl (360 μ mol/l) while only 60 percent (n=15) of the patients in group B had serum urate level of < 6 mg/dl (P = <0.05) as shown in Fig.1



The mean percentage reduction from baseline serum urate concentration at final visit was also greater in Febuxostat group (4.72 mg/dl) than in the Allopurinol group (6.34 mg/dl). Gout flare was reported in 12% (n=3) of group A patients (1 to 2 flares) and 36% (n=9) in group B patients (2 to 3 flares). During the four week prophylaxis period, a significant greater proportion of subjects (n=4, 16%) receiving Allopurinol 300 mg required treatment for a gout flare than those of receiving Febuxostat 80 mg (n=1, 4%). Withdrawal of prophylaxis was initially accompanied by a markedly increased incidence of gout flares in both groups. However, overtime, the percentage of subjects that required treatment for gout flares declined to zero during the 16th week of treatment. Adverse drug reactions were reported in 12% (n=3) of group A patients (nausea, arthralgias,

and rash) while 24% (n=6) in group B (dyspepsia, headache, abdominal pain, diarrhea, and/or pruritic maculopapular rash). The majority of adverse drug reactions were mild or moderate in severity. There were no deaths reported during the study.

DISCUSSION

The cornerstone of gout treatment is achievement of a target serum urate < 6 mg/dl (360 μ mol/l). This therapeutic goal is based on the solubility of urate at 37°C (6.8 mg/dl), levels below which have been associated with lower risk of gout flares and tophi^{12,13}. Lowering serum uric acid levels remains one of the primary goals in the treatment of chronic gout. In our study majority of patients (84%, n=21) in group A (Febuxostat) achieved serum uric acid level of < 6 mg/dl (360 μ mol/l) while only 60 percent (n=15) of the patients in group B (Allopurinol) had serum urate level of < 6 mg/dl (360 μ mol/l) at final visit at 16th week. Two Phase III randomized double-blind trials with Febuxostat have been conducted together in the USA—APEX (Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat)¹⁴ and FACT (Febuxostat versus Allopurinol Control Trial)¹⁵, including a total of 1832 patients. Both studies had similar designs, endpoints and inclusion and exclusion criteria allowing the results to be analysed together. The APEX (Allopurinol and Placebo-Controlled Efficacy Study of Febuxostat) study compared Febuxostat 80, 120 and 240 mg/day with Allopurinol 100 or 300 mg/day (depending on renal function) and placebo over 28 weeks¹⁴. The FACT study compared Febuxostat 80 and 120 mg/day with Allopurinol 300 mg/day over 1 year¹⁵. Both trials showed that Febuxostat was significantly more effective than the conventional dose of 300 mg/day Allopurinol in lowering sUA, as shown by the higher proportion of patients achieving the primary endpoint of sUA < 6 mg/dl (< 360 μ mol/l) at the last three visits. Significantly more Febuxostat-treated patients met the primary endpoint in both studies (48% with 80 mg Febuxostat and 65% with 120 mg Febuxostat in APEX; 53 and 62%, respectively in FACT), compared with those receiving Allopurinol 300 mg (22% in APEX and 21% in FACT; P < 0.001

in both studies). The FACT and APEX studies also showed that Febuxostat was significantly more effective than Allopurinol in reducing sUA in patients with very high pre-treatment sUA levels: of those with sUA at baseline of >10 mg/dl (600 µmol/l), 41% met the primary endpoint with the 80 mg dose and 48% with the 120 mg dose compared with 9% with Allopurinol^{14,15}. The National Institute for Health and Clinical Excellence (NICE) Appraisal Committee focused only on patients receiving Febuxostat (80mg/day titrated to 120mg/day if necessary) with fixed dose Allopurinol (300/100mg/day). And concluded that Febuxostat be recommended as an option for the management of chronic hyperuricaemia in gout only for people who are intolerant to Allopurinol or for whom Allopurinol is contraindicated¹⁶. Cochrane Database used four randomised trials and two open label trial (OLT) with 3978 patients to evaluate the benefits and harms of febuxostat for chronic gout and concluded that Febuxostat at any dose was shown to be beneficial in achieving serum uric acid levels < 6.0 mg/dL and reducing serum uric acid levels in the period from baseline to final visit when compared to placebo and to Allopurinol. However, the grade of evidence ranged from low to high, which indicates that further research is needed¹⁷.

In our study Febuxostat lowered serum uric acid in both gender equally well whereas Chohan and Becker compared the characteristics of female versus male gout patients and assess urate-lowering efficacy and safety of febuxostat or allopurinol treatment in women with gout and found that the percentage of female subjects with sUA levels <6.0 mg/dl at final visit was 0% in the placebo group, 54.3%, 85.1%, 81.0%, and 100.0% in the febuxostat 40 mg, 80 mg, 120 mg, and 240 mg groups, respectively, and 45.9% in the allopurinol group. They concluded that febuxostat 80 mg may be more efficacious than commonly prescribed doses of Allopurinol in female gout subjects with high rates of comorbidities¹⁸.

In our study adverse drug reactions (nausea, arthralgias, and rash) were reported in 12% (n=3) of Febuxostat group whereas 24% (n=6) patients

of Allopurinol group reported adverse drug reactions (dyspepsia, headache, abdominal pain, diarrhea, and/or pruritic maculopapular rash). The majority of adverse drug reactions were mild or moderate in severity. There were no deaths reported during the study. Becker reported five deaths overall, one in each Febuxostat 40 mg and 80 mg groups and three in the Allopurinol group in his 6-month Febuxostat-Allopurinol RCT, involving 2269 receiving 40 mg or 80 mg of Febuxostat daily or Allopurinol(300mg)(200 mg if Creatinine clearance was 30-59 ml/min) daily. Three of the six APTC (Anti Platelet Trialist Collaboration) cardiovascular adverse events were in the Febuxostat 80 mg group and three in the Allopurinol group, with one fatal cardiovascular adverse event in the former and two in the latter¹⁹. One study at College of Pharmacy, University of Iowa reviewed 88 published articles (including 14 human studies) and found that 40 mg/d of febuxostat was noninferior to conventionally dosed Allopurinol (300 mg/d) in the percentage of subjects achieving the primary end point of serum urate <6.0 mg/dL (45% for Febuxostat vs 42% for Allopurinol), whereas 80 mg/d of Febuxostat was reported to be superior (67% vs 42%; P < 0.001). Febuxostat 40 and 80 mg/d appeared to be well tolerated in the populations studied, with adverse events mostly limited to liver enzyme elevations (6.6% and 4.6%, respectively), nausea (1.1% and 1.3%), arthralgias (1.1% and 0.7%), and rash (0.5% and 1.6%)²⁰.

Some limitations need to be considered when interpreting the results of this study. Our sample size may be short and with a shorter follow up period. Additional studies with greater numbers of subjects are needed to verify the results. Longer term studies comparing various doses of Febuxostat and Allopurinol are needed to establish the relative urate lowering and clinical benefits of these agents.

CONCLUSIONS

Although Allopurinol has been widely used for treatment of hyperuricemia, it is associated with inadequate reduction in serum uric acid level and various adverse effects. Febuxostat is potentially a

safe and efficacious alternative causing a sustained reduction in serum uric acid level with infrequent gout flares and adverse drug reactions. We therefore recommend Febuxostat as a drug of choice for patients with chronic gout and hyperuricemia.

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