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Research Article

COMPARISON OF XANTHINE OXIDASE INHIBITORS IN GOUTY PATIENTS WITH HYPERURICEMIA

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ABSTRACT

Objective: Febuxostat is more effective/superior to Allopurinol in reducing the serum uric acid (SUA) level in the treatment of hyperuricemic with gout.

Methods: This randomized control study included 200 hyperuricemic patients with gout, at Multi-center study including Outdoor Departments of Medicine from four different hospitals of Lahore, Pakistan. Patients age range 18-50 years diagnosis with hyperuricemia and gout, SUA >8 mg/dl were included while severe renal impairment and alanine aminotransferase and aspartate aminotransferase patients were excluded from the study.

Results: About 200 patients treated with hyperuricemic with gout were randomly divided into four groups (50%) patients were in each group received different treatment. Out of 200 patients, 118 (59%) were male and 82 (41%) were female with mean age 42.37±9.47 years. Among the Febuxostat group, patients' success rate of lowering SUA level was found to be 32 (64%) as compared to Allopurinol 16 (32%). Drug compliance was similar among treatment groups, i.e. Allopurinol and Febuxostat while the trend toward drug compliance in Allopurinol + Vitamin C and Febuxostat + Vitamin C groups showed similar in number.

Conclusion: Febuxostat is safe and effective to Allopurinol for the treatment of hyperuricemia with gout as the Febuxostat has a significant association with lowering SUA concentration <6 mg/dl. It is concluded that although Febuxostat is safe and effect alone in gouty patients, but it has somehow a little effect with Vitamin C especially in patients who are feeble.

Keywords: Febuxostat, Allopurinol, Serum uric acid.

INTRODUCTION

Hyperuricemia is a biochemical imperfection recognized by serum uric acid (SUA) level more prominent than 6.8 mg/dl [1]. In the greater part of cases (90%), hyperuricemia emerges because of lessened discharge of uric acid by kidneys though in lingering cases (10%) there is expanded the creation of uric acid [2]. The statement of uric acid precious stones is gout. These precious stones structure optional to hyperuricemia that is a serum urate focus more prominent than 0.42 mmol/l [3,4]. The levels of uric acid in the blood rely on two variables. The primary is the rate of uric acid amalgamation in the liver while uric acid outcome from purine corruption and its levels are impacted by both the measure of purines blended in the body and the measure of purines assimilated from the eating regimen. The second determinant of blood uric acid level is the rate of uric acid discharge from the kidneys. The lingering uric acid ventures completely through the digestion systems where microscopic organisms help in its separation. The two medications Febuxostat and Allopurinol are utilized to bring down the SUA level [5]. Xanthine oxidase is the main compound that separates the purine bases and catalyzes the protection of hypoxanthine to xanthine and the xanthine to uric acid. At that point, uric acid is regularly excreted. This chemical inadequacy may be because of the hereditary component, at some point more consumption of purine nourishment and less creation of catalyst. In the event that any medication that is metabolized by xanthine oxidase its activity is expanded by Allopurinol medication like mercaptopurine [6].

Febuxostat was endorsed by the European Medicines Agency on April 21, 2008, and following 1 year it was affirmed by the U.S. Sustenance and Drug Administration on February 16, 2009. Febuxostat brings down SUA focuses by following up on the purine catabolism. The instrument of activity is oxidation of hypoxanthine to xanthine and xanthine to uric acid [6]. Febuxostat is basically very unique in relation to Allopurinol and has a diverse instrument of activity on protein hindrance and is more powerful. Dissimilar to Allopurinol, that experiences oxidation to the dynamic metabolite oxypurinol and connects synthetically with the molybdenum middle of xanthine oxidase. Febuxostat stays unaltered and represses xanthine oxidase by tying in a tight channel prompting the molybdenum focus of the protein. By this component, Febuxostat has the capacity restrain both the lessened and oxidized type of xanthine oxidase to deliver supported decreases in SUA levels [5]. People cannot deliver their own particular Vitamin C and may have developed the ability to secure uric acid to repay for this. Case in point blood uric acid levels in people are when all is said in done around 6 times that of Vitamin C, and around 10 times the levels in different warm-blooded creatures [7]. Like Vitamin C, uric acid has a rule part in protecting high-oxygen tissues (like the mind) from ruin and low blood uric acid levels have been connected with the progression or more prominent than before danger of more than a couple of neurological issue including amyotrophic lateral sclerosis [8], multiple sclerosis [9], and Huntington's [10], Parkinson's [11], and Alzheimer's sicknesses [12].

The reason of this study was to think about the viability of the Febuxostat versus Allopurinol with Vitamin C in the treatment of hyperuricemia with gout. As the writing of the past studies uncovered it is a bit questionable in regards to the adequacy and wellbeing and this study was being led first time in Pakistan. The primary objective of this study is to compare the effectiveness of Febuxostat, Febuxostat plus Vitamin C versus Allopurinol, Allopurinol plus Vitamin C in the treatment of hyperuricemia with gout; and to analyze cost effectiveness among therapies. The secondary objective is to assess any influence of gender on the efficacy of therapies and to record any adverse events caused by any of the therapy.

METHODS

It was hospital–based, multicenter study conducted at Sheikh Zayed Hospital, Lahore; Mian Hospital, Sheikhupura; Jinnah Hospital, Lahore; and Samina Nisar Hospital, Sialkot, Pakistan. 200 patients having hyperuricemia and gout were enrolled in the study. Patients were divided into four groups. To Group I, 50 patients for the treatment of hyperuricemia with gout were given Febuxostat alone. To Group II, 50 patients for the treatment of hyperuricemia with gout were administered Febuxostat and Vitamin C, nonsteroidal anti-inflammatory drug (NSAID)/steroids. To Group III, 50 patients for the treatment of hyperuricemia with gout were given Allopurinol alone and to Group IV, 50 patients for the treatment of hyperuricemia with gout were given Allopurinol and Vitamin C, NSAID/steroids. Simple random sampling technique was applied using balloting method.

Inclusion criteria

Inclusion criteria include both gender (male and female) of ages 18-50 years with a diagnosis of hyperuricemia and gout, SUA >8 mg/dl.

Exclusion criteria

Exclusion criteria include those patients having secondary hyperuricemia or having a severe renal impairment (CrCl <30 ml/minutes). Patients were excluded whose alanine aminotransferase and aspartate aminotransferase values were >1.5 times the upper limit of normal. Patients who take more than 14 alcoholic drinks for 7 days or week drug abuse within 5 years were also excluded from the study [5].

A performa was designed for data collection that includes parameters of the study. Patients with hyperuricemia and gouts SUA >8 mg/dl were randomly assigned by balloting method to receive either Febuxostat or Allopurinol, once a day for 12 months. Patients' physical examination, vital signs, and laboratory tests (SUA, complete chemistry panel, urinalysis, hematology and for women, pregnancy test) were repeated with the compliance at every single month visits during the 12 months treatment period. The primary efficacy endpoint was to achieve patients SUA <6 mg/dl at the final visit. Statistical analysis was performed with SPSS Version 20.0. Continuous variables such as age and SUA levels were reported as mean±standard deviation. Categorical variables such as sex, medical history, and adverse events, were reported as frequencies and percentages. Analysis of variance test was used to compare the efficacy of all treatment groups. p≤0.05 was considered significant.

RESULTS

In this study, total 200 patients were enrolled after taking informed consent. Out of 200 patients, 118 (59%) were males and 82 (41%) were females. For 200 enrolled subjects that were treated for hyperuricemia and gout, the age presentation was 42.37±9.473 years.

In these patients, 70 patients were hypertensive and 130 were non-hypertensive. Overall, 35% patients were hypertensive. As regard to risk factors, diabetes mellitus was found in 26 (13.0%) patients and 174 patients (87.0%) were non-diabetic. The total number of patients that had hyperlipidemia was less commonly observed in 45 (22.5%) patients, and 155 patients did not have hyperlipidemia. Hypercholesterolemia was found less commonly (13%) while 87% patients were found to be non-hypercholesterolemic.

In Group I, total 24 patients (48%) were males and 26 patients (52%) were females, while in Group II 33 patients (66%) were males and 17 (34%) were female; in Group III, 31 patients (62%) were males and 19 (38%) were female; and in Group IV, 30 patients (60%) were males and 20 (40%) were female and found insignificant influence of gender on the efficacy of both therapies as p>0.05 (Fig. 1). While the mean age was 40.04±9.4 years in Group I and 42.74±9.46 years in Group II, 44.76±9.0 years in Group III and 45.48±9.31 years in Group IV, with mild difference patients were found to be older in Group II as compared to other groups. The maximum age of the respondents are 60 years and minimum are 23 years and also showed significant difference with respect to therapies p>0.05 (Fig. 1).

The trend toward mean weight and body mass index was observed to be higher in Group I while mean height was found to be greater in Group II; the difference was statistically insignificant (Fig. 1). As regard to risk factors, diabetes mellitus was more likely to be observed in Group IV as compare to other (16% vs. 14%, 12%, and 10%) (Fig. 1).

In this study, less number of males was involved in the Febuxostat group, and greater number of males was involved in the Febuxostat + Vitamin C group.

Febuxostat was significantly lowering the post-operative SUA level 6.0 mg/dL or less after a 12th month in the treatment of hyperuricemic with gout as compared to Allopurinol as (5.91±1.32 vs. 7.16±1.18). According to the results, time to reducing SUA level achieved in the 12th month post-operative was (Group I; 5.14±1.40, Group II; 6.4±1.24, Group III; 5.91±1.32, and Group IV; 7.16±1.18) (Fig. 2).

Treatment with Febuxostat after 12th months follow-up was effectively reduced serum urate levels in subjects with hyperuricemia and gout as compared to Allopurinol (Fig. 3).

DISCUSSION

Gout is a disease in which there is an increase in the level of SUA and aggregation of sodium monourate precious stone in the joints. This statement will bring about the torment in joints in the night

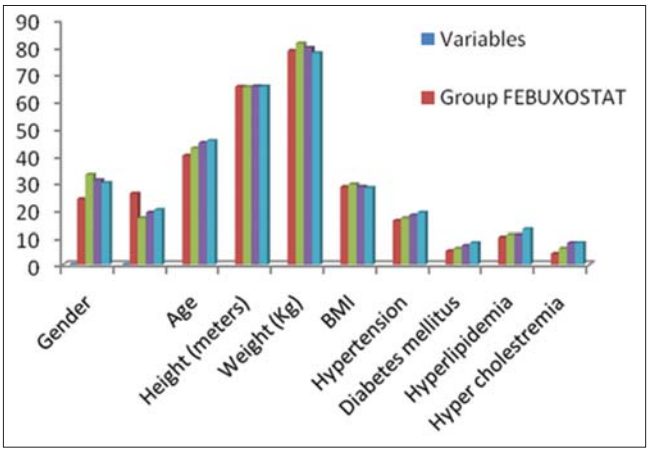

Fig. 1: Descriptive and inferential statistics of patient characteristics with respect to both treatments (Febuxostat versus Allopurinol with Vitamin C) in the treatment of hyperuricemia with gout

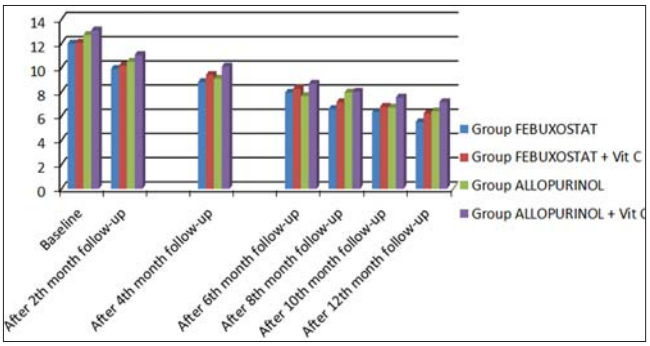

Fig. 2: The graph shows the data of uric acid from baseline and after treatment of 12 months the graph presenting the declining of the uric acid with Febuxostat alone as compared to Allopurinol, Allopurinol + Vitamin C, Febuxostat + Vitamin C

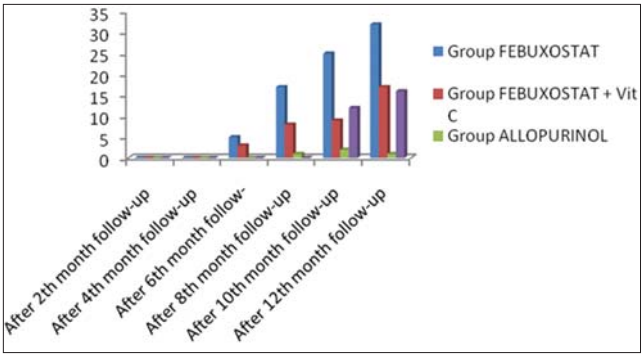

Fig. 3: The graph presenting the data, lowering trend of serum uric acid after the use of uric acid lowering agents and effect in 2nd, 4th, 6th, 8th, 10th, and 12th month, respectively

and increment in the hyperuricemia level in the body. In our study, number enlisted male were 113 and female were just 87 out of 200. The frequency of gout was more basic in men 755 when contrasted with the female 300 in their study on purine utilization of nourishment and fructose drinks more men were selected in a gouty assault when contrasted with female [13]. In our study, there was a little number of females demonstrated danger of gout p<0.001 when contrasted with a male. Choi *et al.* [14] assessed that men are connected with a higher danger of gout (p<0.05) when contrasted with females. Choi *et al.* [13] study was in view of fructose-rich sustenance and the danger of gout in ladies when contrasted with male and worth got was (p<0.001).

Febuxostat assume a promising part in decrease of SUA focus, the impact of the Febuxostat for the treatment of hyperuricemia and gout essentially lessens the SUA level (64%) as contrast with Group II (34%), Group III (2%), and Group IV (32%), while in Group I and Group II the result rates were discovered to be comparative (3%) and in Group III and Group IV muddlings were normal in number (1%). Adverse occasions were not fundamentally distinctive among groups (4% vs. 4%; p>0.05). Our present results were tantamount with the controlled, randomized, double-blind trial (FACT) that looked at the security and adequacy of Febuxostat with Allopurinol patients accomplished SUA, 6.0 mg/dL (53% of patients in the Febuxostat 80 mg/day amass, 62% in the Febuxostat 120 mg/day bunch, and 21% in the Allopurinol 300 mg/day bunch; p<0.001). The rate of antagonistic impacts was comparable between the groups, most generally being liver capacity anomalies, cerebral pain, joint, musculoskeletal, and connective tissue signs and side effects [6].

Febuxostat was mulled over and assessed in various clinical trials having more than 4,000 subjects for up to 5 years. The pervasive, crucial, stage 3 clinical trial, affirmed that Febuxostat was better than Allopurinol (67% vs. 42%) individually at accomplishing SUA <6 mg/dl at the last visit (Khosravan *et al.,* 2007). Likewise, in 2007, Becker *et al*. have likewise directed a study and accomplished viable SUA focus in the 762 selected patients who were treated with Febuxostat that is 45.9% than Allopurinol that is 24% [6]. A further study by Khosravan *et al.* (2007) likewise found that Febuxostat was altogether more noteworthy achieving SUA <6 mg/dl than Allopurinol (67% vs. 42%). Our present results were practically identical with the past writing as dictated by Becker *et al*. (2007) set up that Febuxostat group was huge more viable in lessening the SUA <6 mg/dl as contrast with Allopurinol amass (45.9-53% vs. 21-29%) while in another study post SUA accomplishing was 50% versus 42% and the result were more successive see in Febuxostat group, and no result was found in Allopurinol bunch.

Our study results are additionally in-predictable with these studies. Schumacher *et al*. [15] broke down in 1072 non-randomized controlled subjects (with hyperuricemia and gout) the impacts of Febuxostat versus Allopurinol in decreasing SUA. They found that SUA levels<6mg/dl was accomplished in 72% treated with Febuxostat contrasted and the 46% of the Allopurinol. Following 1 year of treatment, 82% of the patients in all Febuxostat group achieved SUA levels <6 mg/dl, contrasted and 39% of the patients in Allopurinol group. Febuxostat is more viable than Allopurinol in bringing down SUA levels <6 mg/dl as (53% and 48%). The post agent unfavorable occasions in both groups were not measurably critical by Edward [16]. Our outcomes are likewise comparative with this study. Becker *et al.* (2010) found that Febuxostat group was huge more successful in lessening the SUA <6 mg/dl as a contrast with Allopurinol group as (67% and 42%) of patients on Febuxostat 40 mg, 80 mg and Allopurinol, separately. No factual distinction was seen between Febuxostat 40 mg and Allopurinol, and it was considered as non-inferior to Allopurinol; nonetheless, Febuxostat 80 mg was better than both groups (p<0.001). In the groups with a moderate renal disability, Febuxostat 80 mg was predominant (p<0.001) to both 40 mg and Allopurinol (endpoint accomplished in 72%, 50%, and 42%, individually), and Febuxostat 40 mg was barely better than Allopurinol (p<0.021).

Unfavorable occasions were not fundamentally diverse among groups: Allopurinol controlled trial rates were 0.0% for Febuxostat 40 mg and 0.4% (three patients) for both Febuxostat and Allopurinol. One demise happened in each of the Febuxostat groups, contrasted and three trials in the Allopurinol groups. The present study demonstrated a higher rate of unfriendly result 4%, because of the distinctive co-morbid state of the patients. Our outcomes are likewise similar with this study. Goldfarb *et al*. [17] started that Febuxostat was protected and compelling treatment with no unfriendly occasion, lessening urinary uric acid level at 24 hrs versus Allopurinol.

Interestingly with the present study, Kyle *et al*. (2008) analyzed diverse results demonstrated that Allopurinol and Febuxostat were less powerful in diminishing the SUA level <6 mg/dl as 36% and 10%. In a further study, the SUA focus was accomplished in 53% of patients accepting Febuxostat and 21% of those getting Allopurinol (Ignacio *et al*. 2011). This disagreement was because of little sample size. As of late, Ye *et al*. [18] built up that the worthiness of Febuxostat for the treatment of hyperuricemia with gout is like that of Allopurinol (50.9% vs. 45.6%), while the event of unfriendly occasions between the Febuxostat and Allopurinol-treated groups was immaterial. In addition, examine by Ernst and Fravel [19] investigated that there is inconsequential contrast between the viability of both medications in regards to diminishing the SUA level <6 mg/dl as (45% and 42%) while most post-operative unfavorable occasion was found in Febuxostat group as contrast with Allopurinol (9.3% vs. 8.2%). The present study indicated distinctive results because of the patients were experiencing gentle renal hindrance, so both treatments were not as advantageous.

Rather than our study, it was found that there was no proof that Febuxostat is better than Allopurinol for clinically pertinent results. Given its higher expense, Febuxostat ought not to be routinely utilized for ceaseless gout. In this study, it was resolved that Allopurinol lessened the danger of gout flares close around 44% than that of Febuxostat. In general, the antagonistic occasions that were accounted for with Allopurinol were 13% more prominent than that of Febuxostat. Those patients who were receiving Febuxostat accomplished the serum uric level of 6 mg for every deciliter than Allopurinol beneficiaries 92%. Present results indicated distinctive results as present results demonstrated Febuxostat was less powerful 62% (Faruque *et al*., 2013).

In our study, there was additionally diminish in hypertension 19 (38.0%), diabetes 8 (16.0%) p=0.829 and cardiovascular sickness in those patients receiving Allopurinol. Yet, less decline was found in patients those were on Febuxostat hypertension 16 (32.0%) and p=0.9393 and for diabetes 5 (10.0%) and for Allopurinol hypertension p=0.829 and diabetes p=0.939. At the same time, Goicoechea *et al.* (2010) showed that Allopurinol treatment decreases the danger of cardiovascular occasions in 71% contrasted and standard treatment.

Choi *et al.* (2006) recommended that Vitamin C diminished the danger of gout in men, multivariate hazard for gout in men taking Vitamin C was 0.83 and those not allow Vitamin C, the multivariate hazard for gout were 0.66 or more noteworthy p<0.01. However, in our study, those men were bringing Vitamin C in blend with Vitamin C the danger component were p<0.293. Teixeira *et al.* [20] built up that the Vitamin C supplementation has influenced SUA diminishment. The impact was more noteworthy on subjects with a pattern SUA level more noteworthy or equivalent to 4.85 mg/dl. On these subjects, the SUA level was lessened by 0.78 mg/dl.

In our study, we analyzed the adequacy of Febuxostat and Allopurinol with Vitamin C, while Stamp *et al.* [21] looked at Vitamin C and Allopurinol in gout patients, yet in our study, we additionally utilized recently affirmed medication. In our study, the better result in control of SUA for 12 month treatment was with Febuxostat 17 (34.0%) and with Febuxostat and Vitamin C 32 (64.0%) and that with Allopurinol 18 (36.0%) and Stamp *et al.* (2013) their outcome with the Allopurinol alone p=0.82 and in the Vitamin C in addition to Allopurinol group; p<0.029, with Vitamin C result, were 34 (68.0%). Furthermore, 500 mg Vitamin C is well over the suggested day by day stipend of Vitamin C of 90 mg/day in men and 75 mg/day in women. The dose of Vitamin C utilized as a part of this study (500 mg/day) was in light of that utilized as a part of past studies. Vitamin C brought about a noteworthy increment in urate discharge, with no distinction between those with and those without gout [21].

CONCLUSION

In our study, we compared Febuxostat and Allopurinol plus Vitamin C in their combination so as to achieve the better therapy for patients. With reference, Febuxostat is safe and effective to Allopurinol for the treatment of hyperuricemia with gout as SUA concentration >6 mg/dl returns to near normal values in the majority of patients with SUA level <6 mg/dl after receiving Febuxostat treatment as compared to Allopurinol. It is concluded that although Febuxostat is safe and effect alone in gouty patients, but it has somehow a little effect with Vitamin C especially in patients who are feeble.

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