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Comparison of Allopurinol And Febuxostat in Asymptomatic Hyperuricemic Patients and their Impact on Serum Creatinine

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ABSTRACT

Objective: To determine the effect of Allopurinol & Febuxostat for the treatment of hyperuricemic patients & its influence on renal function by measuring serum creatinine level.

Study Design & setting: The clinical trial was conducted at Dr. Ruth K M Pfau Civil Hospital, Karachi, during the period of September 2018 to March 2019

Methodology: 60 patients with sUA > 6.8 mg/dl were registered. A detailed history was taken, patient's baseline serum Uric Acid (sUA) & serum Creatinine were measured. Patients were divided into two groups to receive Allopurinol, 300 mg & Febuxostat 80 mg, daily for 90-days. The blood parameters were repeated at day 30 and 90.

Results: Group-A (Allopurinol treated patients) baseline uric acid changed from mean 8.79 ± 0.98 mg/dl to 6.40 ± 0.86 mg/dl at day 90. In Group-B (Febuxostat treated patients) sUA baseline mean changed from 8.85 ± 0.97 mg/dl to 5.96 ± 0.68 mg/dl. Mean difference ± SD change of serum uric acid in Group-A was 2.39 ± 1.15 mg/dl and with Group-B it was 2.90 ± 0.87 mg/dl. Mean Serum Creatinine in Group-A changed from 1.54 ± 0.39 mg/dl to mean 1.48 ± 0.40 mg/dl compared with Group-B where it changed from 1.42 ± 0.30 mg/dl to 1.45 ± 0.31 mg/dl at day-90. Mean difference ± SD of serum Creatinine in Group-A was 0.11 ± 0.25 mg/dl & in Group-B it was, 0.03 ± 0.15 mg/dl. The above changes were statistically non-significant with p-value of 0.144.

Conclusion: Allopurinol and Febuxostat treatment resulted in improvement of serum Uric Acid levels while maintaining their renal function.

Key words: Allopurinol, Febuxostat, Serum uric acid, Serum creatinine.

INTRODUCTION:

Recent data have shown that hyperuricemia and gout are increasing worldwide. Since the last 40-years there has been a continuous rise in the incidence of hyperuricemic population around the world[1]. The international prevalence rate of hyperuricemia is 0.3% with a 90% male predominance, while 10 to 20% of patients exhibit a family history.[2]

Hyperuricemic patients present with a serum urate concentration above 6.8 mg/dL at which crystals are retained, cause severe damage to joint structures and are associated with poor kidney and cardiovascular outcomes [3].

The intrinsic sources of uric acid are degradation of purines by xanthine oxidase in the liver, intestine & muscles, while extrinsic sources are fatty meat, organ meat, and seafood [4].

Approximately 70% of daily production of urate is eliminated by the kidneys, and the remaining is expelled in the feces. However, the gastrointestinal passage of urate tries to overcome the reduced excretion by the kidneys during renal failure [5].

It seems that there is a close association between creatinine and uric acid synthesis. Uric acid is known to cause endothelial dysfunction, vascular smooth muscle cell proliferation, increased IL-6 synthesis, and impairment of nitric oxide production, all of which may contribute to the progression of chronic kidney disease.[6]

Uric acid may be associated with chronic kidney diseases through several mechanisms, direct renal toxicity, and hyperuricemia exacerbating other risk factors for kidney disease or it may be a marker of the severity of other risk factors, like diabetes and the metabolic syndrome [7].

Allopurinol, a xanthine oxidase inhibitor, is given orally and a commonly applied drug in hyperuricemia treatment, owing to its efficacy and good tolerability. Allopurinol is quickly oxidized by XO to hypoxanthine and xanthine, respectively. Allopurinol at low concentrations is competitive

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inhibitor and at higher concentrations is a noncompetitive inhibitor of xanthine oxidase enzyme. Allopurinol, as an antioxidant, scavenge free radicals such as hydroxyl radical and superoxide anion. Therapeutic applications, later first Phase-I human studies were carried out, following several years of laboratory studies [8].

Febuxostat, also a xanthine oxidase inhibitor, is a selective, non-purine derivative that was approved by the FDA in 2009 for its prolonged duration of action. It's efficacy in hyperuricemia and gout with potent urate lowering properties are documented.[9]

Febuxostat is metabolized by microsomal enzyme system in the liver, either actively oxidized and produces inactive acylglucuronide metabolites. Kidney excretes more or less 50% of the administered Febuxostat and only 10% as unchanged form of drug. Allopurinol hypersensitivity syndrome (AHS) is a rare but potentially serious risk for 2–8% of patients[10]. The rationale of therapy was to treat hyperuricemia with therapeutic doses of Allopurinol 300 mg/day & Febuxostat 80 mg/day, hoping to reduce the serum uric acid over long term, prevent relapses and have a beneficial impact on renal function by measuring serum creatinine levels.

METHODOLOGY

The study approved from BASR & ERB of Hamdard University, was conducted at Medical OPD, Dr. Ruth K M Pfau Civil Hospital, Karachi. Patients of either sex, ages varying from 38 to 69 years, having a serum uric acid concentration > 6.8 mg/dl and fulfilling the inclusion and exclusion criteria were registered after obtaining an informed and written consent. All available patients who met the study inclusion & exclusion criteria were included in this analysis.

Seventy [70] patients from Medical OPD were interviewed during the period of six months from Sept 2018 to March 2019; of these sixty patients were registered and divided into two groups, A & B, each having 35 patients. All patient data was entered in the designed pro forma. During follow up 10 patients, 5 from each group, dropped out due to irregularity in visits and poor adherence to drug.Group-A, was treated by Allopurinol (Zyloric) 300 mg once daily for 90 days Group-B, was treated by Febuxostat (Go-Uric) 80 mg daily for 90 days.

Patient details about serum uric acid & serum creatinine were recorded from baseline to day 90 in case recording file (CRF). All collected data of scheduled visits was entered for final statistical analysis.

Data was collected and processed on SPSS version 22. Results were described as percentages. One sample t-test paired sample test and Chi-square were used to determine the mean and standard deviation. P value <0.05 was taken as significant.

RESULTS:

In Group-A thirty registered patients completed the study duration with Allopurinol treatment for 90-days, with the following baseline characteristics; males 22 (73.3%), mean age 57.60 + 6.11 years (range 45 to 68 years), mean body weight 63.27 + 5.74 kg, 16 (53.3%) smokers, mean serum uric acid 8.79 + 0.98 mg/dL, mean serum creatinine 1.54 + 0.39 mg/dL. [Table-1] Group-B registered thirty patients had the following baseline characteristics; 21 (70%) male, 9 (30%) females mean age 54.30 + 8.66 years (range 40 years to 69 years), mean body weight 65.03 + 7.22 kg, 13 (43.3%) smokers, mean serum uric acid 8.85 + 0.97 mg/dl & mean creatinine 1.48 + 0.40 mg/dl. [Table-1]

Group-A (Allopurinol 300 mg/daily): The change in mean serum uric acid from day-0 to day-90 was 8.79 + 0.98 mg/dL to 6.40 ± 0.86 md/dl [p value < 0.001, with percentage change of 27%, mean serum creatinine 1.54 ± 0.39 mg/dl to 1.42 ± 0.30 mg/dl [p value < 0.019], with percentage change of 8%. [Table-2]

Group-B (Febuxostat 80 mg/daily): The change in mean serum uric acid from day-0 to day-90 was 8.85 ± 0.97 mg/dl to 5.96 ± 0.68 mg/dl [p value < 0.001], percentage change was 33%, mean serum creatinine 1.48 ± 0.40 mg/dl to 1.45 ± 0.31 mg/dl [p value < 0.258], with percentage change of 2%. [Table -2] Mean difference ± SD for change of serum uric acid in Group-A was 2.39 ± 1.15 mg/dl with Group-B mean was 2.90 ± 0.87 mg/dl. Regarding this decrease there was no significant statistical difference between Allopurinol & Febuxostat with p-value 0.061. Mean difference ± SD, for change of serum Creatinine in Group-A was 0.11 ± 025 mg/dl. & Group-B, 0.03 ± 0.15 mg/dl. There was no significant statistical difference between Allopurinol & Febuxostat with p-value 0.144. Table-3

Adverse reactions in the study Group-A were reported in 9 out of 30 patients and in Group-B, 4 out of 30 patients. [Table-4]

Table-1: Comparison of baseline characteristics of group-A & group-B in hyperuricemic patients

	Group-A n=30	Group-B n=30
GENDER		
• **Female**	8 (26.7%)	9 (30%)
• **Male**	22 (73.3%)	21 (70%)
Age in years (Mean+SD)	57.60 ± 6.11	54.30 ± 8.66
Smokers	16 (53.3%)	13 (43.3%)
Non-Smokers	14 (46.7%)	17 (56.7%)
Body Weight Kg	63.27 ± 5.74	65.03 ± 7.22
Serum Uric Acid mg/dl	8.79 ± 0.98	8.85 ± 0.97
Serum Creatinine mg/dl	1.54 ± 0.39	1.48 ± 0.40

Group- A: Allopurinol 300 mg once daily, Group-B: Tab Febuxostat 80 mg daily, n= Number of Patients

Table-2
Comparison of serum uric acid & serum creatinine between Group-A & Group-B in hyperuricemic patients. (Day -0 and Day -90)

Group A (Allopurinol)	Day	Mean ± SD	P-value*
Serum Uric acid mg/dl	Base line (Day – 0)	8.79 ± 0.98	< 0.001**
	After treatment (Day – 90)	6.40 ± 0.86	
	Percentage Change	27%	
Group B (Febuxostat)			
Serum Uric acid mg/dl	Base line (Day – 0)	8.85 ± 0.97	< 0.001**
	After treatment (Day – 90)	5.96 ± 0.68	
	Percentage Change	33%	

Group A (Allopurinol)	Day	Mean ± SD	P-value*
Serum Creatinine mg/dl	Base line (Day – 0)	1.54 ± 0.39	< 0.001**
	After treatment (Day – 90)	1.42 ± 0.30	
	Percentage Change	8%	
Group B (Febuxostat)			
Serum Creatinine mg/dl	Base line (Day – 0)	1.48 ± 0.40	< 0.001**
	After treatment (Day – 90)	1.45 ± 0.31	
	Percentage Change	2%	

* Dependent or Paired t test
** Significant

Table-3 Comparison group A & B for Change in Serum Uric Acid level (Day -0 and Day -90)

Group A & B	Mean Difference ± SD	P-value*
Group A	2.39 ± 1.15	0.061
Group B	2.90 ± 0.87	

Comparison group A & B for Change in Serum Creatinine level

Group A & B	Mean Difference ± SD	P-value*
Group A	0.11 ± 0.25	0.144
Group B	0.03 ± 0.15	

Table-4 Adverse Effects Of Allopurinol & Febuxostst

Adverse effect of drugs	Response	Group-A Allopurinol 30mg0		Group-B Febuxostat 80mg	
		No.	%	No.	%
Abdominal pain	Yes	03	10	00	00
	No	27	90	30	100
Palpitation	Yes	02	6.7	00	00
	No	28	93.3	30	100
Hematuria	Yes	02	6.7	01	3.3
	No	28	93.3	29	96.7
Hypersensitivity	Yes	02	6.7	00	00
	No	28	93.3	30	100
Numbness	Yes	00	00	01	3.3
	No	30	100	29	96.7
Headache	Yes	00	00	01	3.3
	No	30	100	29	96.7
Vomiting	Yes	00	00	01	3.3
	No	30	100	29	96.7
Fever	Yes	00	00	00	00
	No	30	100	30	100
Fatigue	Yes	00	00	00	00
	No	30	100	30	100

DISCUSSION:

Hyperuricemia prevalence not only is reported in developed countries but evidence is also coming from the low and middle-income countries and incidences are continuously rising. Evaluation of an epidemiological study conducted on healthy volunteers for over seven years showed that raised serum uric acid increases the risk for new outbreaks of kidney function impairment. [11]

The prevalence of hyperuricemia is 1–4%. In European countries, with male predominance 3–6% & 1–2%in female, as the age advances prevalence rises to 10% & 6% respectively in both sexes. Yearly incidence is 2.68 per 1000 persons, being 2-6 times greater in males.[12]

Hyperuricemia pathophysiology is not clearly known, imbalance of breakdown of purines and uric acid excretion is answerable to its action. Most cases of hyperuricemia present clinically because of faulty urate excretion. Raised serum uric acid is now established as a potential risk factor for developing number of disturbances. Hyperuricemia in the initial days was recognized as gout, but now it is considered as a separate entity and responsible for number of metabolic and hemodynamic abnormalities.[13]

The present study demonstrates that with Allopurinol treatment, the serum uric acid reduced from a mean of 8.79 + 0.98 mg/dl to a mean of 6.40 + 0.86 mg/dl on day 90, total percentage change being 27% and mean serum creatinine reduced from a mean of 1.54 ± 0.39 mg/dl to a mean of 1.42 ± 0.30 mg/dl, percentage change being 8%. These findings are in agreement with the study conducted by Becker, 2005.[14]

In renal dysfunctions a better option is to start with the minimum dose. A reduced initial target dosage in renal impairment is still defended but studies suggest that when unable to obtain desired effects, the dosage may be increased above the present guidelines. In our study, the renal function

assessment was within normal limits and Allopurinol therapy did not influence the serum Creatinine level; these findings are in agreement with those of 2007.[15]

In a clinical trial conducted by Whelton 2011 in which Febuxostat was used, significant change in serum creatinine was found, which is in agreement with our study [16]. Similarly, a study conducted by Kanbay et al showed that treatment with Allopurinol led to decrease in serum creatinine after 3 months [17].

Study conducted by Perez-Ruiz, 2000 validated that higher doses of Allopurinol are more effective in decreasing concentration of uric acid, but Allopurinol 300 mg adequately decreased uric acid concentration without influencing the renal functions; these results matched with our study[18].

Use of Febuxostat by Grassi for short period of 1 to 6 months duration significantly reduced the serum uric acid concentrations. Our study findings are in agreement with Grassi.[19].

Becker[9], conducted clinical trial of 52 weeks duration using Febuxostat and Allopurinol, in which serum uric acid was reduced to 6.0 mg/dL during the first 3 months; these findings matched with our results in the reduction of serum uric acid at day 90 with the change being more marked with Febuxostat than Allopurinol.

Our study also agrees with Borghi, 2016 [20] who reported, that in hyperuricemia, Febuxostat is a suitable option and should be considered as a first line drug as, it has provided safe and efficient effects in clinical studies.

In a study of 28-weeks by Schumacher[21], conducted with different doses, Febuxostat more adequately reduced and maintained serum urate levels < 6.0 mg/dl than Allopurinol, at doses 300 & 100 mg or placebo in hyperuricemic patients and gout, with mild to moderate renal dysfunction. In our study, Allopurinol 300 mg/day & Febuxostat 80 mg/day productively decreased serum uric acid without any disturbance of renal function with better effects reported in Febuxostat group of patients.

A clinical study conducted in patients with hyperuricemia and gout by Michael in 2005, using Febuxostat and Allopurinol showed reduction in serum uric acid levels[22]. In our study Febuxostat 80 mg, daily more effectively reduced the serum uric acid concentration that is 39%, compared with Allopurinol 300 mg daily that showed 27% reduction.

Kamatani[23] conducted a comparative study of Allopurinol & Febuxostat in doses 200 mg & 40 mg/day respectively for the period of 44 days and showed that Febuxostat at 40 mg/daily demonstrated more potent hypouricemic effects than Allopurinol at 200 mg/day. In our study Febuxostat 80mg/day & Allopurinol 300mg/day for 90 days demonstrated that Febuxostat is more potent than Allopurinol in hyperuricemia.

Similarly, the CONFIRMS trial conducted by Becker [24] and using Febuxostat significantly reduced serum uric acid levels in a 6-month study of 2269 patients with normal renal function.

Frampton[25] pointed that earlier studies have identified cardiovascular toxicities with Febuxostat; ongoing trials are in progress to identify the cardiovascular safety of Febuxostat versus Allopurinol. In our 90-day study sixty hyperuricemic patients were monitored for drug safety. We observed no serious adverse events related to drugs used during the study period except for abdominal pain, palpitations and hematuria in patients on Allopurinol, all of which were easily self-controlled.

Study conducted for short duration and limited number of patients, poor adherence, non-compliance, illiteracy and poor socio-economic issues are some important limiting factors.

CONCLUSION:

Febuxostat was superior to Allopurinol in reducing serum uric acid as well as reducing serum creatinine in asymptomatic hyperuricemia patients. Furthermore, no serious adverse events were seen in our study proving the safety of the drugs.

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