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Research Paper

COMPARATIVE EVALUATION OF EFFICACY AND SAFETY PROFILE OF FEBUXOSTAT WITH ALLOPURINOL IN PATIENTS WITH HYPERURICEMIA AND GOUT

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Gout is known to be a metabolic disease mostly affecting the elderly. Treatment and management becomes all the more difficult in this age group because of presence of co-morbidity (like Hypertension, Diabetes Mellitus, Renal and Cardiovascular diseases) and concomitant use of medication which at times do not agree with the usual hypouricemic drugs used in gout. The objective of this study was to compare the effect and side effect of Allopurinol with Febuxostat, a relatively new uric acid lowering drug. Subjects between 30 - 55 years having serum uric acid level > 8.0 mg were enrolled in this randomized trial to receive either Allopurinol (100 mg thrice a day) or Febuxostat (40 mg once daily) for a period of 3 months. Febuxostat (40 mg once daily) was more effective than Allopurinol (100 mg thrice a day) in lowering serum uric acid at 3 months. Serum uric acid came below 6 mg/dl in >62% of Febuxostat treated patients as compared to Allopurinol group where it came down in only <38% of cases. Flaring of gouty arthritis was nil in Febuxostat group while 7 patients showed drug related problem in Allopurinol group. Compliance to drug therapy was much better in Febuxostat group.

Key words: Gout, Febuxostat, Allopurinol, Efficacy, Adverse effect

INTRODUCTION

Gout is a medical condition usually characterized by recurrent attacks of acute inflammatory arthritis—a red, tender, hot, swollen joint. It is caused by elevated levels of uric acid in the blood (Wortmann, 2002), which crystallizes and deposits in joints and surrounding tissues. The metatarsal-phalangeal joint at the base of the big toe is the most commonly affected. However, it may also present as tophi or urate nephropathy. Gout in yesteryear was incorrectly known as the “disease of kings”, rich food which only the rich can afford was considered the etiological factor. In fact, its risk factors vary. Recent studies indicate that the incidence is increasing; has almost doubled and is affecting the younger age

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group. It now affects 1-2% of the Western population due to longer life expectancy and changes in diet and sedentary life style (Roddy *et al*., 2007; Matthew and danda, 2004). Hyperuricemia is the underlying cause of gout which depends on diet, genetic predisposition, overproduction or underexcretion of urate. Renal underexcretion of uric acid is the primary cause of hyperuricemia in about 90% of cases, while overproduction is the cause in less than 10% (Richette and Bardin, 2010).

Apart from change in life style and diet modification, Urate lowering therapy (ULT) is usually started at and above 7 mg/dl of serum uric acid to prevent urate crystal deposition (Yamanaka *et al*., 1998). The much prescribed drug in this category is Allopurinol which is a structural isomer of hypoxanthine and is an inhibitor of the enzyme xanthine oxidase (Catton *et al*., 2006). This enzyme is responsible for the successive oxidation of hypoxanthine and xanthine, resulting in the production of uric acid. Allopurinol has to be started at 100 mg once daily, gradually increasing to 100 mg thrice a day because some patients may be hypersensitive to the drug, requiring careful monitoring. It may also produce potentially fatal adverse effects like fever, skin rash, eosinophilia, hepatitis, renal function abnormality, and, in some rare cases Stevens–Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TENS) (Stamp *et al*., 2012). More common is a less-serious rash that may lead to discontinuing this drug. Allopurinol may also produce bone marrow depression, leading to aplastic anemia. It can also cause peripheral neuritis and interstitial nephritis. It has teratogenic potential too and is contraindicated in pregnancy (Maria *et al*., 2013).

Febuxostat is a non-purine selective inhibitor of xanthine oxidase which works by non-competitively blocking the xanthine oxidase Co factor (Takano *et al*., 2005; Becker *et al*., 2004). It is very safe, no adverse drug effect have been reported so far at 40 mg once daily (Backer *et al*., 2010).

The present study was to find out the comparative serum uric acid lowering efficacy of these drugs and their adverse effect if any.

METHODS

Selection of Patients

The study was performed at a tertiary care hospital in Kanpur from Sept'2009 to March'2013. After approval of institute's ethics committee an informed consent was discussed, approved and signed by all volunteers. Subjects reporting to our hospital took part in this study. Eligibility criteria were (a) age (yrs): 35-55; (b) weight: 45-75 kg; (c) diagnosed of hyperuricemia of > 8 mg/dl; (d) requiring starting of urate lowering therapy. Exclusion criteria included (a) previous or existing cardiovascular, hepatic or renal disease; (b) persons taking diuretics; (c) diabetes mellitus; (d) history of alcohol consumption; (e) family history of allergic disorder and prior history of any arthritic problem. All thus selected volunteers had their blood drawn up for laboratory test which included complete blood count, C-reactive protein, Renal and liver function test, Rheumatoid factor, fasting blood sugar and serum uric acid. The patients thus selected were randomly assigned to take either 100 mg of Allopurinol or 40 mg of Febuxostat. Two increments of 100 mg each were made in Allopurinol group at day 10 and day 20, i.e., at the end of 3 weeks all patients in this group

were taking 300 mg of Allopurinol daily (100 mg thrice a day).

Follow Up

A team of health professional visited them and ensured that volunteers were taking regular medication and adhering to diet advised. Patients were made aware of the problems they might experience while taking these drugs. They were encouraged to not only to report about these but to any physical and mental problem encountered during therapy. The same sets of laboratory tests were performed after 3 months of therapy.

Not only the % change in serum uric acid level but also the adverse effect profiles were compared at the end point of the study.

STAT ANALYSIS

The data thus obtained was evaluated by using the statistical Package for Social Science (SPSS v. 16). Statistical analysis of data was performed by chi-square test.

RESULTS

Out of 506 patients only 414 patients completed the study in 3 years, 238 in Febuxostat group and 176 in Allopurinol group. Out of 238 in Febuxostat group, all showed decline in serum uric acid but in 148 patients it came down to below 6 mg/dl (62.18%). In Allopurinol group this was only 40.3%, i.e. in only 71 patients out of 176 serum uric acid came down to acceptable level (Table 1). The response of Febuxostat on lowering serum uric acid was significantly more than Allopurinol (p-value <0.0001) (Table 2).

We did not encounter any problem in Febuxostat group, no patient reported of any adverse effect. In Allopurinol group, 7 patients had

Table 1: Treatment * Response Cross Tabulation

			Response (Serum uric acid)		Total
			<6 mg/dl	>6 mg/dl	
Treatment	Febuxostat	Count	148	90	238
		Expected Count	125.9	112.1	238.0
		% within Treatment	62.2%	37.8%	100.0%
		% within Response	67.6%	46.2%	57.5%
	Allopurinol	Count	71	105	176
		Expected Count	93.1	82.9	176.0
		% within Treatment	40.3%	59.7%	100.0%
		% within Response	32.4%	53.8%	42.5%
	Total	Count	219	195	414
		Expected Count	219.0	195.0	414.0
		% within Treatment	52.9%	47.1%	100.0%
		% within Response	100.0%	100.0%	100.0%

Table 2: Chi-Square Tests

	Value	df	Asymp. Sig.(2-sided)	Exact Sig.(2-sided)	Exact Sig.(1-sided)
Pearson Chi-Square	19.376[a]	1	.000		
Continuity Correction[b]	18.510	1	.000		
Likelihood Ratio	19.495	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	19.330	1	.000		
N of Valid Cases[b]	414				

Note: [a] 0 cells (.0%) have expected count less than 5. The minimum expected count is 82.90; [b] Computed only for a 2 x 2 table

to discontinue the drug; 4 for skin rashes with pruritus , 2 for rashes with Fever and generalized myalgia and 1 for arthritic problem.

DISCUSSION

Gout like hypertension and diabetes mellitus is the curse of modern civilization and life style. In coming years more and more persons are going to be affected by this malady requiring an effective and safe drug. The drug available to lower uric acid falls broadly into 3 categories, uric acid production inhibitor, uric acid excretion (uriosouric) and uric acid metabolizer (Schlesinger, 2004).

Uricosouric drugs like probenecid are not effective in cases of compromised renal function, may produce urate crystal precipitation, have many other ADRs and are generally avoided as 1st line drug.

Uric acid metabolizers (uricase) are a new line of drugs which metallizes uric acid to soluble allantoin which is easily excreted. However, these drugs are indicated in refractory cases; are very costly and are to be administered parenterally. In short, not the drug for the masses (Sherman *et al*., 2008).

Allopurinol (production inhibitors) has remained the drug of choice of gout for > 5 decades. The new drug, Febuxostat is also a production inhibitor but it affects the co factor of xanthine oxidase (Khosravan *et al*., 2004; Mayer *et al*., 2005).

CONCLUSION

In uric acid production inhibitors, Febuxostat scores much better than Allopurinol. At 40 mg once daily, it was found to be virtually safe, more efficacious and cost effective than Allopurinol 100 mg thrice a day.

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