A comparative study of efficacy and safety of febuxostat and allopurinol in pyrazinamide-induced hyperuricemic tubercular patients

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Abstract:

Objectives: To compare the efficacy and safety of febuxostat and allopurinol in pyrazinamide (PZA)-induced hyperuricemia in patients taking antitubercular therapy (ATT).

Methods: This randomized controlled study was conducted at a tertiary care teaching institute of Rajasthan in all the sputum-positive tubercular patients aged between 18 and 65 years of either sex. Serum uric acid level was monitored at 0th, 2nd, 4th, 6th, and 8th week of ATT. Patients whose uric acid level was found to be increased at 2nd week were finally recruited in the study. Ninety patients who developed hyperuricemia due to ATT were divided randomly into three groups (Group A - febuxostat, Group B - allopurinol, and Group C - control) of thirty patients each. Mean serum uric acid levels were calculated at all the weeks in all the groups, and serum uric acid levels were compared by applying student’s t-test and ANOVA.

Results: Mean serum uric acid level decreased from 10.698 mg/dl (at 2nd week) to 7.846 mg/dl (at 8th week) in Group A and from 11.34 mg/dl (at 2nd week) to 7.280 mg/dl (at 8th week) in Group B. Numbers of adverse events encountered across both the treatment groups were same with both the drugs.

Conclusion: Allopurinol and febuxostat were equally efficacious in lowering PZA induced raised serum uric acid level in tubercular patients, and it was possible to continue ATT without withdrawing PZA.

Key words: Allopurinol, antitubercular therapy, febuxostat, hyperuricemia

Tuberculosis (TB) is one of the oldest diseases and is considered as major cause of suffering and death since times immemorial. It is prevalent not only in the developing countries including India but also in the developed world.[1] In India, it kills two persons every three minutes, nearly 1000 every day.[2] Treatment of TB consists of multiple drugs of which pyrazinamide (PZA) is an important constituent.[3] Its coadministration with other drugs led to a one-third reduction in the duration of therapy, i.e. 6 months short-course chemotherapy and two-third reduction in relapses of TB cases.[4]

Hyperuricemia is defined as a plasma (or serum) urate concentration 6.8 mg/dl.[5] The risk of developing gouty arthritis or urolithiasis increases with higher urate levels.[5] Many drugs are known to induce hyperuricemia including PZA.[6,7] Usually, serum uric acid levels return to normal after withdrawal of the offending drug. Nevertheless, it can be tried that antitubercular therapy (ATT) can be continued without stopping PZA and decreasing the serum urate levels with the help of serum uric acid-lowering drugs. Two classes of urate-lowering drugs currently available are uricosuric agents and xanthine oxidase inhibitors. Probenecid inhibits tubular secretion of rifampicin. PZA and ethambutol may interfere with uricosuric action of probenecid, so probenecid cannot be used concurrently with these drugs for lowering serum uric acid level.

Therefore, allopurinol and febuxostat seem to be possible candidates to be used as uric acid-lowering agents in tubercular patients. Allopurinol, a xanthine oxidase inhibitor, is generally a safe, effective, and well-tolerated...
drug. Rarely, life-threatening rashes and/or severe multisystem allopurinol hypersensitive reactions are encountered.\[8-10\] Febuxostat is a newer xanthine oxidase inhibitor without such adverse effects. Febuxostat is not indicated in the secondary hyperuricemia.\[11\] Review of literature revealed that no studies have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch–Nyhan syndrome or malignant disease or in organ transplant recipients); therefore, it is not recommended for use in these patients.\[11\] Hence, an initiative was taken to use febuxostat in the treatment of drug-induced hyperuricemia and to compare it with another drug allopurinol of the same category. Hence, this study was undertaken with the aim of reducing PZA-induced hyperuricemia with the help of urate-lowering drugs and comparing the efficacy and adverse effects of allopurinol with febuxostat for the same purpose in patients taking ATT. This study also compared the costs of the two drugs, which is one of the important parameters for patients’ compliance, especially in developing countries like India.

Materials and Methods
This randomized controlled study was conducted in a tertiary care teaching institute of Rajasthan after taking approval from the Institutional Ethics Committee. Data were collected in the approved pro forma after taking written consent of the patient. All the sputum-positive tubercular patients aged between 18 and 65 years of either sex without history of any osteoarthritic condition and intake of any other hyperuricemic drugs were included in the study in whom standard four-drug ATT was given. Patients having hepatic dysfunction, history of renal calculi, pregnant, and lactating females were excluded from this study.

Serum uric acid level was monitored at 0\(^\text{th}\), 2\(^\text{nd}\), 4\(^\text{th}\), 6\(^\text{th}\), and 8\(^\text{th}\) week of ATT. Patients whose uric acid level was found to be increased at 2\(^\text{nd}\) week were finally recruited in the study. Ninety patients who developed hyperuricemia due to ATT were divided randomly into three groups (Group A, Group B, and Group C) of thirty patients each. Group A was treated with febuxostat and Group B with allopurinol at a daily dose of 40 and 300 mg, respectively. Group C was kept as control. Mean serum uric acid levels were calculated at all the weeks in all the groups, and serum uric acid levels were compared by applying student’s t-test and ANOVA.

Results
A total of ninety patients were recruited in this study who developed hyperuricemia after 2 weeks of starting ATT, of which sixty patients were male and thirty patients were female. The mean age of the patients was 41.5 years (ranging from 18 to 65 years).

Mean serum uric acid levels were calculated, and it was found that serum uric acid levels increased sharply at 2\(^\text{nd}\) week in all the Groups A, B, and C as shown in Table 1.

Mean serum uric acid level decreased from 10.698 mg/dl (at 2\(^\text{nd}\) week) to 7.846 mg/dl (at 8\(^\text{th}\) week) in Group B. The mean levels decreased significantly at 4\(^\text{th}\), 6\(^\text{th}\), and 8\(^\text{th}\) weeks when compared with mean values at 2\(^\text{nd}\) week. However, when values at 8\(^\text{th}\) week were compared with baseline (at 0\(^\text{th}\) week) values, the difference was still significant which suggests that drugs were able to decrease serum uric acid level but could not attain the baseline level. It was observed that at 8\(^\text{th}\) week, 63.33% of patients were having serum uric acid level >6 mg/dl and 53.33% of patients were having >6.76 mg/dl in Group A, and in Group B, 70% of patients were having serum uric acid level >6.0 mg/dl and 53.33% of patients were having >6.8 mg/dl at 8\(^\text{th}\) week.

The mean serum uric acid levels at all the weeks, i.e. 0\(^\text{th}\), 2\(^\text{nd}\), 4\(^\text{th}\), 6\(^\text{th}\), and 8\(^\text{th}\) week were compared by applying student’s t-test between Group A and B, Group A and C, and Group B and C and were found to be nonsignificant at all the weeks. When the ANOVA was performed for all the weeks within the three groups, it was found to be insignificant [Table 2].

Table 1: Mean uric acid levels at various weeks in all the groups

| Groups | Mean serum uric acid level | Baseline serum uric acid | After antitubercular therapy | After drug intervention |
|--------|---------------------------|--------------------------|------------------------------|-------------------------|
|        | 0\(^\text{th}\) week | 2\(^\text{nd}\) week | 4\(^\text{th}\) week | 6\(^\text{th}\) week | 8\(^\text{th}\) week |
| A (febuxostat) | 4.772 | 10.698 | 9.026 | 7.917 | 7.846 |
| B (allopurinol) | 5.397 | 11.34 | 9.1810 | 8.2790 | 7.280 |
| C (control) | 4.533 | 8.302 | 9.2253 | 9.8833 | 10.74 |

\(^*\)P>0.5 (nonsignificant) when t-test was applied between Group A and B, A and C, and B and C at all weeks

Table 2: Comparison of serum uric acid level during weeks in various groups

| Weeks | Groups | Number of patients | Mean serum uric acid | P* |
|-------|--------|--------------------|----------------------|----|
| 0\(^\text{th}\) | C | 30 | 4.533±1.2669 | >0.05 |
| A | 30 | 4.772±1.3106 |
| B | 30 | 5.397±1.0350 |
| Total | 90 | 4.735±1.2888 |
| 2\(^\text{nd}\) | C | 30 | 10.698±1.9089 | >0.05 |
| A | 30 | 8.302±2.5627 |
| B | 30 | 11.336±2.0763 |
| Total | 90 | 8.859±3.0770 |
| 4\(^\text{th}\) | C | 30 | 9.2253±3.20732 | >0.05 |
| A | 30 | 9.026±1.83503 |
| B | 30 | 9.1810±2.14980 |
| Total | 90 | 8.2063±2.66509 |
| 6\(^\text{th}\) | C | 30 | 7.9717±2.20173 | >0.05 |
| A | 30 | 7.8339±2.46383 |
| B | 30 | 8.2790±2.33157 |
| Total | 90 | 7.8339±2.60659 |
| 8\(^\text{th}\) | C | 30 | 10.743±2.4574 | >0.05 |
| A | 30 | 7.846±3.1104 |
| B | 30 | 7.280±2.2619 |
| Total | 90 | 7.813±2.9705 |

\(^*\)P>0.05 (nonsignificant) when ANOVA was applied between Groups A, B, and C at all weeks. ANOVA = Analysis of variance
One patient responded well to febuxostat but developed hypersensitivity (developed itching after starting the drug which subsided after stopping it) to it and was switched to allopurinol but did not respond to allopurinol. One patient who was treated with febuxostat, uric acid lowered only slightly but responded well to allopurinol. Serum uric acid level increased in spite of taking febuxostat in one patient but responded well to allopurinol. One patient developed hypersensitivity to allopurinol (developed itching and rashes after taking the drug which subsided after stopping it). In one patient, allopurinol was not able to reduce serum uric acid level to a great extent and hence switched over to febuxostat and responded well. One patient responded well to febuxostat whose serum uric acid level increased in spite of taking allopurinol.

Expenditure of the patient on including either of the two drugs was compared, and the difference was calculated.

Cost of allopurinol (100 mg) was Rs. 2.33/tablet, and it has to be taken thrice daily, i.e. cost/day was found to be Rs. 6.99. Cost of febuxostat (40 mg) was Rs. 7.70/tablet, and it has to be taken once daily, i.e. the cost/day was found to be Rs. 7.70. Difference between the two drugs was found to be 71 paise/day or Rs. 21.30/month.

Discussion

TB was virtually wiped out with the help of antibiotics which were developed in 1950s, but the disease resurfaced in potent new and dangerous forms such as multidrug-resistant TB and extensive drug-resistant TB. PZA is an important constituent of ATT but at times forcing its withdrawal due to hyperuricemia.

In this study, an attempt was made to continue ATT without withdrawing PZA with the help of adding drugs which decrease synthesis of uric acid by inhibiting xanthine oxidase enzyme. A number of previous studies including three randomized controlled trials have been conducted to compare the two drugs in patients of gout and hyperuricemia, and results were in favor of febuxostat. Results of our study suggested that it was possible to continue PZA in the patients with the help of these drugs. Both drugs were found to be equally efficacious in lowering the serum uric acid levels possibly the reason for same efficacy might be the same mechanism of action of inhibiting the synthesis of uric acid by inhibiting xanthine oxidase. According to Singal et al. study, febuxostat is a great addition to the armamentarium for gout management particularly in patients in whom allopurinol has failed because of either lack of efficacy or due to adverse events because of intolerance to allopurinol. Moreover, a committee of the British National Institute for Health and Clinical Excellence concluded that although febuxostat is found to be more effective than fixed-dose (300 mg) allopurinol, it had not been found to be clinically more efficacious or cost-effective than allopurinol. However, the committee recommended febuxostat for people who are intolerant of allopurinol.

Numbers of adverse events encountered across both the treatment groups were same with both the drugs. Similar studies have shown same results.

Allopurinol is known to cause severe hypersensitivity reactions, but after reviewing literatures, it was discovered that such reactions are usually seen after long-term administration of the drug. The Phase III trials and long-term follow-up also showed the incidence of adverse events with febuxostat to be similar with that of allopurinol.

The reasons for no or little response with febuxostat could be explained on the basis of that the dose was not increased further. No response with either of the two drugs can also be explained because of variation in response due to individual variation in metabolizing the drugs. Possibility of poor patient compliance cannot be neglected. Perhaps, the patient has not taken the drug and giving false history.

Overall cost of treatment with two drugs was almost same with negligible difference. Favorable point for using febuxostat could be that it requires only once-daily administration resulting in better patient compliance. Moreover, overall incidence of adverse effects is also few with febuxostat according to previous studies as compare to allopurinol. As stated earlier that a committee of the British National Institute for Health and Clinical Excellence also concluded that it had not been shown to be clinically more efficacious or cost effective than allopurinol and recommended febuxostat for people who are intolerant of allopurinol.

Conclusion

This study concludes that both allopurinol and febuxostat were equally efficacious in lowering PZA induced raised serum uric acid level in tubercular patients, and it was possible to continue ATT without withdrawing PZA in patients who developed hyperuricemia due to it. Similar studies are required in future because ethambutol, constituent of ATT, also known to increase serum uric acid levels in about 50% of patients was not considered in the present study. Other factors such as genetic predisposition and genetic polymorphism could also affect, and alter serum uric acid levels have not been taken into consideration in our study.

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Conflicts of Interest
There are no conflicts of interest.

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