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Dr. Rithvic Kevin P
Department of Orthopaedics, Dev Hospitals, Bhongir, Telangana, India

Dr. Vishnu Senthil
Department of Orthopaedics, Government Royapettah Hospital, Chennai, Tamil Nadu, India

Dr. Manish Khanna
Department of Orthopaedics, Mayo institute of Orthopaedics, Lucknow, Uttar Pradesh, India

Corresponding Author:
Dr. Rithvic Kevin P
Department of Orthopaedics, Dev Hospitals, Bhongir, Telangana, India

Navigating the choice between topiroxostat and febuxostat for hyperuricemia management: A prospective comparative study

Dr. Rithvic Kevin P, Dr. Vishnu Senthil and Dr. Manish Khanna

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Abstract
Hyperuricemia is a metabolic condition associated with various health complications, including gout, kidney disease, and cardiovascular events. Topiroxostat and febuxostat are two commonly prescribed xanthine oxidase inhibitors for managing hyperuricemia, yet there is a paucity of direct comparative studies evaluating their efficacy and safety profiles. To address this gap, we conducted a prospective, randomized, open-label, parallel-group trial involving 50 patients diagnosed with hyperuricemia. Patients were randomly assigned to receive either topiroxostat or febuxostat for a duration of 12 weeks. Primary outcome measures included changes in serum uric acid (SUA) levels, while secondary outcomes encompassed renal function parameters and incidence of adverse events. Our findings indicate that both topiroxostat and febuxostat effectively reduced SUA levels over the treatment period, with no significant difference observed between the two groups. However, topiroxostat demonstrated a more significant reduction in serum creatinine levels, urinary albumin excretion, and improvement in estimated glomerular filtration rate (eGFR) compared to febuxostat. Safety profiles were favorable for both medications, with no serious adverse events reported. These results suggest that while both topiroxostat and febuxostat are effective in lowering SUA levels, topiroxostat may offer additional renal protective benefits. Further comparative studies are warranted to elucidate the clinical implications and optimal use of these medications in hyperuricemia management.

Keywords: Hyperuricemia, topiroxostat, febuxostat, serum uric acid

1. Introduction
Hyperuricemia, characterized by high levels of uric acid in the blood, is a metabolic condition that has gained significant attention due to its association with gout, kidney disease, and cardiovascular events. As a purine metabolite, uric acid contributes to the formation of monosodium urate crystals in joints and tissues, leading to inflammation and pain in gout patients.

Beyond its direct role in gout pathogenesis, hyperuricemia has emerged as an independent risk factor for hypertension, chronic kidney disease, and metabolic syndrome, highlighting the need for effective management strategies. Topiroxostat and febuxostat are both xanthine oxidase inhibitors commonly prescribed for hyperuricemia, with the former being relatively newer to the market. Topiroxostat has shown promising results in lowering uric acid levels in patients with gout, a common condition associated with hyperuricemia. On the other hand, febuxostat has been a staple treatment option for individuals intolerant to allopurinol or with severe gout symptoms. While both medications aim to reduce uric acid levels by inhibiting xanthine oxidase, there is a paucity of direct comparative studies evaluating their efficacy and safety profiles. Understanding the similarities and differences between topiroxostat and febuxostat could aid clinicians in making informed decisions regarding the optimal treatment for hyperuricemia based on individual patient characteristics and comorbidities. Further research is essential to determine the comparative effectiveness of these two medications in managing hyperuricemia [2]. The need for comparative efficacy of topiroxostat and febuxostat in its management, considering the potential impact on reducing gout flares and preventing long-term complications. Therefore, a comprehensive study comparing the two drugs is imperative to optimize treatment outcomes in hyperuricemia patients [2].

2. Materials and Methods

2.1 Study Design: This study is designed as a prospective, randomized, open-label, parallel-group trial conducted at DROTC, Hyderabad.

2.2 Study Population: Patients diagnosed with hyperuricemia, defined as serum uric acid levels exceeding 7mg/dl, will be recruited for this study.

2.3 Inclusion criteria

Age greater than 18 years and Willingness to give consent

2.4 Exclusion criteria

- Secondary causes of hyperuricemia like Tumour lysis syndrome, Lesch Nyhan syndrome etc.
- Renal function impairment(egfr ≤ 30 mL/min/1.73 m^2)
- Liver impairment
- Allergies to Topiroxostat or Febuxostat.
- Treatment with mercaptopurine hydrate or azathioprine
- Pregnancy

2.5 Randomization and Allocation: 50 eligible patients are randomly assigned in a 1:1 ratio to topiroxostat and febuxostat group using computer-generated randomization codes. Allocation concealment is ensured using sealed, opaque envelopes.

2.6 Interventions

- Topiroxostat Group: 25 Patients allocated to this group will receive oral topiroxostat at a starting dose of 160 mg/day for 4 weeks followed by 80mg/day for 8 weeks
- Febuxostat Group:25 Patients allocated to this group will receive oral febuxostat at a starting dose of 80 mg/day for 4 weeks followed by 40mg/day for 8 weeks
- The decision to give Topiroxostat double the dose of febuxostat is made from taking previous studies into consideration.

Lee yojin and etal evaluated that an equivalent outcome would be achieved by febuxostat 83.33 mg or topiroxostat 150 mg [3].

Kazuomi Kario in his study on Comparative effects of topiroxostat and febuxostat on arterial properties in hypertensive patients with hyperuricemia gave febuxostat and topiroxostat at dosages of 10-60mg/dl and 40-160mg/dl respectively [4].

Similar dosages has been used by Akira Sezai in the TROFEO study [5].

2.7 Study Duration: The study is conducted over a 6 month period, including a screening phase, a treatment phase, and a follow-up period (3 months).

2.8 Outcome Measures

Primary Outcome:

Change in serum uric acid (SUA) levels from a baseline to the SUA levels at the end of 12 weeks after the initiation of treatment.

Secondary Outcomes

- Proportion of patients achieving target serum uric acid levels.
- Change in renal function parameters (e.g., serum creatinine, estimated glomerular filtration rate, UACR) from a baseline by the end of the 12 week treatment period.
- Incidence of adverse events and treatment discontinuations due to adverse events.

2.9 Statistical Analysis: Data is analyzed on an intention-to-treat (ITT) basis. Descriptive statistics are used to summarize baseline characteristics and outcome measures. Continuous variables are analyzed using t-tests or non-parametric tests, as appropriate. Categorical variables are analyzed using chi-square tests or Fisher's exact tests. Statistical significance is set at $p < 0.05$.

2.10 Ethical Considerations: The study is conducted in accordance with the principles outlined in the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Informed consent is obtained from all participants prior to enrolment, and patient confidentiality is maintained throughout the study.

3. Results

3.1 Patient Characteristics: A total of 50 patients were registered meeting the inclusion criteria. Out of them, 25 were allocated to topiroxostat and febuxostat groups respectively. There were 1 dropout from the Topiroxostat group and 3 dropouts from the Febuxostat group. So a total of 24 patients in Topiroxostat and 22 patients in Febuxostat group were studied. The patient characteristics are illustrated in Table 1.

The comparison between the Topiroxostat group and Febuxostat groups revealed several insights. Firstly, there was no significant difference in the average age of participants between the two groups, indicating a balanced distribution in age demographics. However, a notable difference emerged in gender distribution, with the Febuxostat group showing a significantly higher proportion of male participants compared to the Topiroxostat group.

On the other hand, parameters such as BMI, serum uric acid levels, serum creatinine levels, UACR spot test results, and eGFR values exhibited no significant discrepancies between the two groups. Moreover, when considering various risk factors such as diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, cerebrovascular disease, obesity, and smoking habits, the differences between the groups were not statistically significant. These findings suggest that while gender distribution varied, other key clinical parameters and risk factors remained comparable between individuals treated with Topiroxostat and Febuxostat.

3.2 Primary End Point

The changes in Serum Uric acid (SUA) levels are shown in Fig. 1 and Table 2.

The SUA level was significantly decreased by the administration of topiroxostat and Febuxostat (p value<0.05), and the decrease in SUA level was maintained even after 3months (Fig. 1).

Among 24 patients with SUA > 7.0 mg/dL at baseline and 3 months after topiroxostat administration, 18 patients (75%) had SUA $\leq$ 6.0 mg/dL. Similarly, 17 patients (77%) out of 22 patients attained SUA $\leq$ 6.0 mg/dL after 3 months of treatment with Febuxostat.

Table 1: Patient characteristics

Variable	Topiroxostat group(n=24)	Febuxostat Group (n=22)	P value
Age (years)	44.9 ± 10.78 years	45.54 ± 11.57	0.88108[b]
Sex male: female	14:10	15:7	0.00000[b]
BMI kg/m^2	25.67 ± 2.98	25.26±2.57	0.61714 [b]
Serum Uric acid (mg/dl)	8.35±1.12	8.2±0.75	0.60095 [b]
Serum creatinine (mg/dl)	1.26±0.15	1.23±0.16	0.54010[b]
UACR spot test (mg/gcr)[a]	23.86±4.24	22.8±4.43	0.44981 [c]
eGFR (mL/min/1.73 m^2)	80.3±16.02	83.33±18.26	0.51232.[b]
Risk factors n (%)			
Diabetes mellitus	9(37.5)	6(27)	0.36085 [b]
Hypertension	12(50)	7(31)	0.14606 [b]
Dyslipidaemia	6(25)	7(31)	0.75169 [b]
Chronic kidney disease	4(16)	3(13)	0.44932 [b]
Cerebrovascular disease	2(8)	0(0)	0.30641 [b]
Obesity	4(16.6)	2(9)	0.22856 [b]
Smoking	8(33)	9(40)	0.76877 [b]

Mean ± SD or n (%)
BMI Body mass index
UACR urinary albumin-to-creatinine ratio
eGFR estimated glomerular filtration rate
[a]UACR were listed a geometric mean and 95% confidence interval
[b]Student's *t* test
[c]Student's *t* test after logarithmic transformation.

Table 2: Changes in SUA before and after treatment with Topiroxostat and febuxostat

Time	SUA (mg/dl) Topiroxostat Group	SUA (mg/dl) febuxostat group
Before Treatment	8.35±1.12	8.2±0.75
At 1 week	7.41±0.85	7.4±0.63
At 6 weeks	6.56±o.77	6.62±0.63
At 12 weeks	5.67±0.89	5.65±0.65

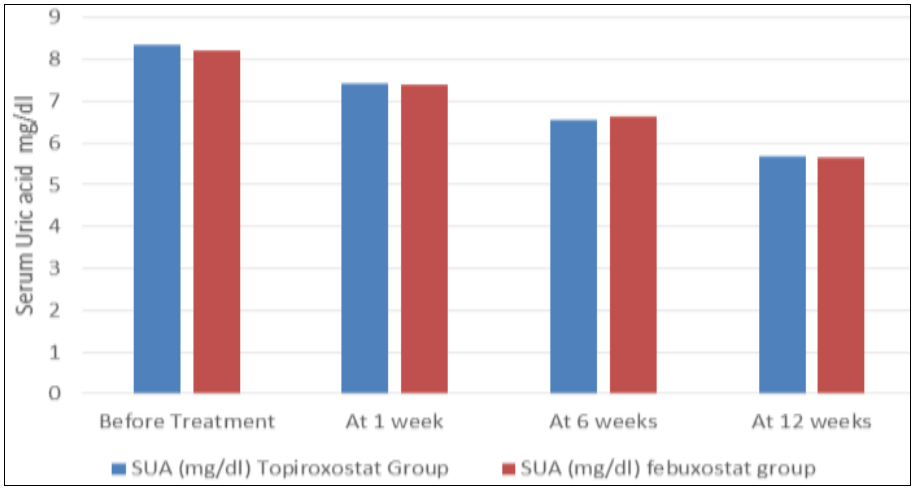

Fig 1: Changes in SUA before and after treatment with Topiroxostat and febuxostat

However there was no significant difference in SUA between the 2 groups either before or after treatment with p value of 0.929.

3.3 Secondary End Points

3.3a Serum Creatinine: Serum creatinine decreased in all patients from a base line of 1.266±0.15 mg/dl in the Topiroxostat group and 1.236±0.16 mg/dl in the Febuxostat group to 1.249±0.15 mg/dl in Topiroxostat group and 1.23±0.15 mg/dl in the Febuxostat group at the end the of 12 week treatment period respectively as shown in Table 3 and Figure 2.

However, the reduction of serum creatinine was statistically significant with p value of 0.00012 and mean reduction of 0.0173 mg/dl in the Topiroxostat group.

Even though there was a mean reduction of 0.0066 mg/dl in the Febuxostat group but the p value of 0.06427 was not significant.

Table 3: Changes in Serum Creatinine before and after treatment with Topiroxostat and febuxostat.

Time	Serum Creatinine (Topiroxostat group) mg/dl	Serum Creatinine (Febuxostat group) mg/dl
Before Treatment	1.266±0.15	1.236±0.16
At 1 week	1.257±0.14	1.224±0.15
At 6 weeks	1.253±0,14	1.225±0.15
At 12 weeks	1.249±0.15	1.23±0.15

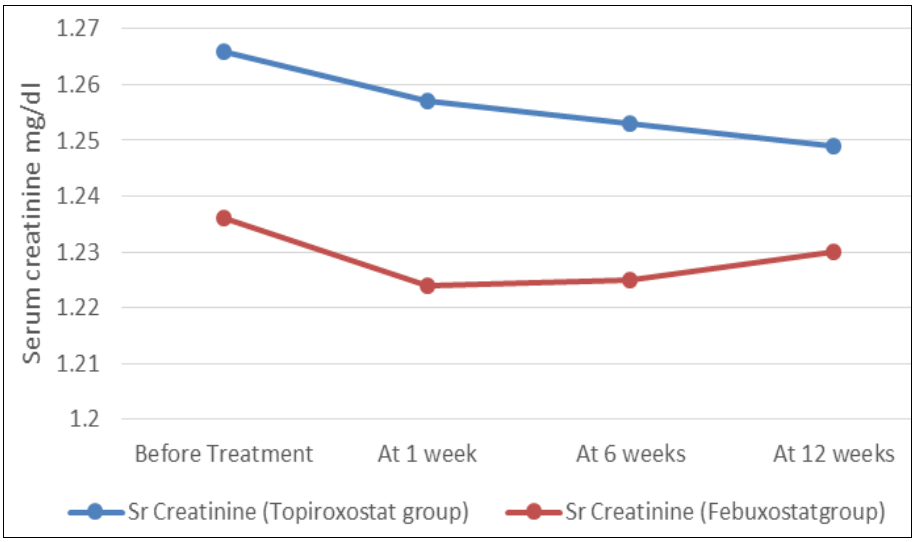

Fig 2: Treatment with Topiroxostat and febuxostat

3.3b eGFR: Before treatment initiation, the mean eGFR was 80.3 ± 16.02 mL/min/1.73m^2 for the Topiroxostat group and 83.33 ± 18.26 mL/min/1.73 m^2 for the Febuxostat group respectively. After 12 weeks of treatment, the mean eGFR was 81 ± 16.14 mL/min/1.73 m^2 for the Topiroxostat group and 83.80 ± 18.16 mL/min/1.73 m^2 for the Febuxostat group respectively. (Table 4, Figure 3)

The improvement of eGFR values in Topiroxostat over the 12- week period is statistically significant, with a mean improvement of 0.6375 mL/min/1.73 m^2 and a p value of 0.00034.

However, there was no significant change in eGFR before and after treatment in the Febuxostat group.

Table 4: Changes in eGFR before and after treatment with Topiroxostat and Febuxostat.

Time	eGFR Topiroxostat Group (mL/min/1.73 m^2)	eGFR Febuxostat Group (mL/min/1.73 m^2)
Pre Treatment	80.3±16.02	83.33±18.26
At 12 weeks Treatment	81±16.14	83.80±18.16

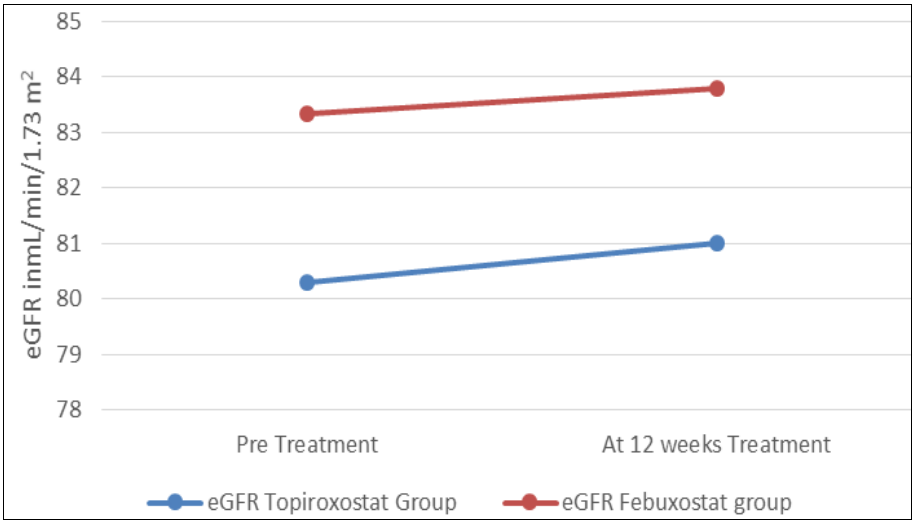

Fig 3: Topiroxostat and Febuxostat

3.3c UACR: In the Topiroxostat group at baseline, the mean UACR was 23.8±4.24 mg/gcr. As treatment progressed, a gradual decrease in UACR was observed: at 1 week, the mean UACR decreased to 22.8±3.86 mg/gcr, followed by further reductions to 22.39±3.66 mg/gcr at 6 weeks and 21.76±3.51 mg/gcr at 12 weeks. This trend suggests a consistent and significant improvement in urinary albumin excretion, with a mean reduction of 2.09±1.41 mg/gcr over the 12-week treatment period with Topiroxostat. (P value 0.0000)

Before treatment initiation, the mean UACR was 22.86 ± 4.43 mg/gcr. Across subsequent time intervals, including 1 week, 6 weeks, and 12 weeks into the treatment regimen, there were minimal fluctuations in the UACR levels: 22.52±4.42 mg/gcr, 22.67±4.62 mg/gcr, and 22.71±4.55 mg/gcr, respectively. These findings indicate that there were no substantial changes in urinary albumin excretion over the 12-week treatment period with Febuxostat, suggesting a consistent UACR profile throughout the duration of the study. (Table 5, Figure 4)

Table 5: Changes in UACR before and after treatment with Topiroxostat and Febuxostat.

Time	UACR mg/gcr TOPIROXOSTAT Group	UACR mg/gcr FEBUXOSTAT Group
Before Treatment	23.8±4.24	22.86±4.43
At 1 week	22.8±3.86	22.52±4.42
At 6 weeks	22.39±3.66	22.67±4.62
At 12 weeks	21.76±3.51	22.71±4.55

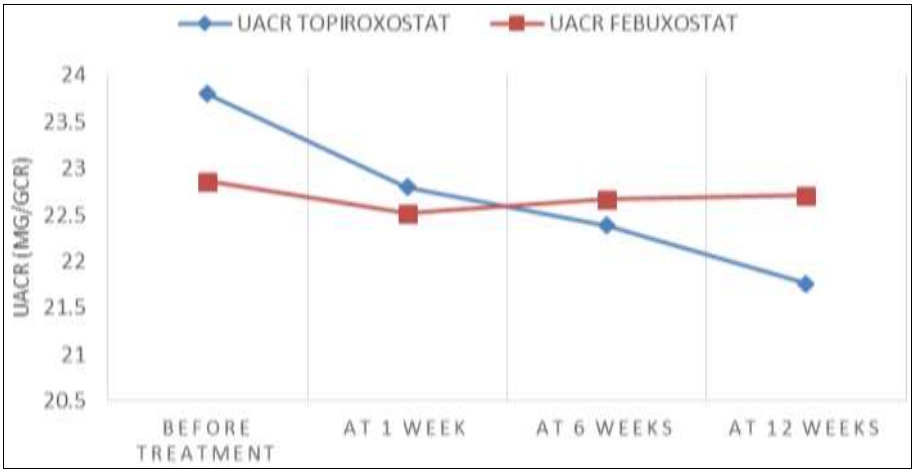

Fig 4: Topiroxostat and Febuxostat

Safety: There were no serious adverse events after the administration of Topiroxostat and Febuxostat.

4. Discussions

In India, the prevalence of hyperuricemia estimated in 2018 was 25.8%, with an increased prevalence in diabetics, hypertensives, and diabetic hypertensives [6]. The association between elevated serum uric levels (SUA) and cardiovascular diseases has long been documented in the epidemiological database [7].

Furthermore, chronic kidney disease has also been proven to have an independent association with the increase in uric acid levels [8]. So aggressive and timely treatment to lower hyperuricemia is the need of the hour.

Our study comparing efficacy of the newer molecule Topiroxostat with the already established Febuxostat showed that both molecules are equally effective in reducing serum uric acid levels. The administration of both Topiroxostat and Febuxostat resulted in a significant decrease in serum uric acid (SUA) levels (p-value < 0.05), and this reduction was sustained even after three months of treatment, as depicted in Figure 3. Among the 24 patients with baseline SUA levels exceeding 7.0 mg/dL who received Topiroxostat, 18 patients (75%) achieved SUA levels of ≤ 6.0 mg/dL after three months. Similarly, among the 22 patients who received Febuxostat, 17 patients (77%) attained SUA levels of ≤ 6.0 mg/dL after the same treatment duration. However, despite these individual treatment effects, there was no statistically significant difference in SUA levels between the two groups either before or after treatment, with a p-value of 0.929. This suggests that while both medications effectively lowered SUA levels in hyperuricemia patients, they did so to a comparable extent, without a discernible difference between the two treatment groups. Similarly, according to the TROFEO study [5] there was no significant difference in serum uric acid levels between the Topiroxostat and febuxostat groups either before or after treatment, but they also concluded reduction of serum uric acid was more rapid with febuxostat than topiroxostat which was not present in our study.

In our study, both the Topiroxostat and Febuxostat cohorts exhibited a decrease in serum creatinine levels over a span of 12 weeks. Specifically, in the Topiroxostat group, levels decreased from a baseline of 1.266±0.15 mg/dl to 1.249±0.15 mg/dl at the 12-week mark, while in the Febuxostat group, they decreased from a baseline of 1.236±0.16 mg/dl to 1.23±0.15 mg/dl at the same interval. Notably, the reduction observed in the Topiroxostat group was statistically significant (p = 0.00012, mean reduction of 0.0173 mg/dl). Although the Febuxostat group showed a mean reduction of 0.0066 mg/dl, the p-value (0.06427) did not reach significance. These findings suggest that Topiroxostat may be more effective than Febuxostat in reducing serum creatinine levels.

The Topiroxostat group displayed a noteworthy reduction in UACR over the course of 12 weeks (Mean reduction: 2.09±1.41 mg/gcr, p< 0.0001). Conversely, minimal fluctuations in UACR levels were observed in the Febuxostat group during the treatment period, indicating negligible changes in urinary albumin excretion. Kenjiro Kimora *et al*. concluded that compared to placebo, febuxostat did not mitigate the decline in kidney function among patients with stage 3 CKD and asymptomatic hyperuricemia [13]. Additionally, Kario K *et al*. in 2021 found that while urinary albumin-creatinine ratio (UACR) significantly decreased from baseline to 24 weeks with topiroxostat (-20.8%; p = 0.021), it did not significantly change with febuxostat (-8.8%; p = 0.362) [14]. However, findings from the TROFEO CKD trial study suggested that febuxostat demonstrated more potent renal protective effects than topiroxostat [15].

The eGFR analysis from Table 4 indicates a statistically significant improvement in eGFR values within the Topiroxostat group over the 12-week period, with a mean improvement of 0.6375 mL/min/1.73 m^2 and a p-value of 0.00034. This suggests that treatment with Topiroxostat led to a notable enhancement in renal function among participants within this group. Conversely, there was no statistically significant change in eGFR before and after treatment in the Febuxostat group, implying that Febuxostat did not have a significant impact on renal function over the same treatment duration. These findings underscore the differential effects of

Topiroxostat and Febuxostat on eGFR levels and highlight the potential superiority of Topiroxostat in promoting renal function improvement among individuals with similar baseline characteristics. Similarly, a study by Yuta Tezuka in 2018 has concluded that Topiroxostat, not Febuxostat, could improve eGFR in hypertension patients [17]. Additionally a study by Satoh Etal revealed Topiroxostat and Febuxostat could improve eGFR in hypertension patients, and moreover, Topiroxostat could reduce UACR [16].

However, Kenjiro kimura [13] also found that there was no significant difference in mean eGFR slope between the febuxostat (0.23±5.26 mL/min/1.73 m2 per year) and placebo (−0.47±4.48 mL/min/1.73 m2 per year) groups.

Long-term administration of Uric acid-lowering drugs is required in patients with hyperuricemia; therefore, safety is also an important clinical problem. A total of 46 patients in this study were able to receive topiroxostat and febuxostat for over 3 months, and there were no adverse events or abnormal liver function. The long-term (12-month) efficacy and tolerability of topiroxostat have been further confirmed in an observational study conducted in over 4000 patients [9]. The CONFIRMS trial also confirmed that Febuxostat at 40mg and 80 mg is safe at all levels of renal function [10]. However, findings from the CARES trial in 2018 [11], concluded that mortality and cardiovascular mortality were higher with febuxostat than with allopurinol. Nonetheless, a recent study by Hoon Jeong and etal concluded that febuxostat was not associated with a higher risk of cardiovascular disease than allopurinol [12].

5. Strengths of the study

- **Comparative Analysis**: The study conducts a thorough comparative analysis between Topiroxostat and Febuxostat, providing valuable insights into their efficacy and safety profiles in managing hyperuricemia.
- **Longitudinal Assessment**: The study evaluates the effects of both medications over a 12-week period, allowing for the assessment of sustained treatment outcomes.
- **Comprehensive Outcome Measures**: Various outcome measures, including serum uric acid levels, serum creatinine levels, urinary albumin excretion, and estimated glomerular filtration rate (eGFR), are assessed, providing a comprehensive understanding of the medications' effects on renal function.
- **Clinical Relevance**: The study addresses clinically relevant endpoints such as renal function improvement, contributing to the practical management of hyperuricemia and associated comorbidities.

6. Limitations of the study

- **Sample Size**: The sample size of the study may be relatively small, potentially limiting the generalizability of the findings.
- **Short Duration**: The study duration of 12 weeks may not capture long-term treatment effects or complications associated with prolonged medication use.
- **Single-Center Study**: If conducted at a single center, the study's results may not reflect broader population demographics or healthcare practices.

7. Conclusion

In conclusion, both Topiroxostat and Febuxostat demonstrated effectiveness in reducing serum uric acid levels, with sustained reductions observed over three months of treatment. While both medications similarly lowered serum uric acid levels, Topiroxostat showed a more significant reduction in serum creatinine levels and urinary albumin excretion compared to Febuxostat, indicating potential renal protective effects. Topiroxostat also exhibited a significant improvement in eGFR, highlighting its potential superiority in enhancing renal function. The Safety profiles were favourable for both drugs in the study, suggesting long-term tolerability. Further comparative studies may be warranted to elucidate the clinical implications and optimal use of these medications in hyperuricemia management.

8. Source of funding: None.

9. Conflict of interest: None.

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