ORIGINAL ARTICLE

A single-centre experience of febuxostat as a second-line urate-lowering therapy

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Abstract

Introduction: The purpose of this study was to describe the local experience in terms of drug efficacy and safety using a new xanthine oxidase inhibitor, febuxostat, as a second-line urate-lowering therapy (ULT) in gout patients with normal renal function and chronic kidney disease.
Methods: This cross-sectional study included all gout patients who attended the rheumatology clinic from January 2013 to June 2018 and had received febuxostat as a second-line ULT. Analysis focused on the proportion of gout patients who achieved target serum urate (sUA) of <360 μmol/L, duration taken to achieve target sUA, and febuxostat dosage at achievement of target sUA. Safety assessments included comparison of serum creatinine, estimated glomerular filtration rate (eGFR), and serum alanine aminotransferase (ALT) at baseline, at achievement of target sUA, and at 12-monthly intervals.
Results: Majority (90.9%) of patients achieved target sUA. Median duration required to achieve target sUA was 5.5 months with IQR (interquartile range) of 8.5. Five (22.7%) patients achieved target sUA within one month of therapy with febuxostat 40 mg per day. Eleven (55%) patients achieved target sUA within six months and 16 (80%) by 12 months. Equal proportion of patients achieved target sUA with febuxostat 40 mg per day and 80 mg per day, respectively. There was no significant difference in the changes in serum creatinine level, eGFR and ALT from baseline and at achievement of target sUA, nor at 12-monthly intervals throughout the duration of febuxostat therapy. Apart from three patients who developed hypersensitivity reactions to febuxostat, no other adverse events were reported.
Conclusion: A significant proportion of gout patients with CKD managed to achieve target sUA with a lower dose of febuxostat at 40 mg per day and it is reasonable to maintain this dose for up to six months before considering dose escalation.

Introduction

Gout is the most common inflammatory arthritis in adults worldwide, and if left untreated can lead to joint deformities and a poor quality of life.[1,2] Over the last several decades, the incidence of gout has risen substantially, mainly due to increased frequency of comorbidities that are related to hyperuricemia, including obesity, hypertension, diabetes mellitus, dyslipidemia and chronic kidney disease (CKD).[3-6] The growing use of drugs that induce hyperuricemia, such as thiazide and loop diuretics, is further contributing to the rise in gout cases.

Gout is attributed to hyperuricemia, which is defined as serum urate (sUA) concentration exceeding 400 μmol/L – the limit of urate solubility. The recommendation in gout management is to lower and maintain sUA to a level below 360 μmol/L[7] in order to avoid formation of monosodium urate crystals and deposition in joints and soft tissues, thus minimizing gout flares. This treat-to-target concept is key to quality management of gout. Most gout patients require urate-lowering therapy (ULT), with allopurinol being the most frequently used agent.[8] It is a xanthine oxidase inhibitor that reduces urate production. Allopurinol is generally safe and well tolerated. Nevertheless, it occasionally induces serious cutaneous adverse reactions which can be potentially fatal. Patients intolerant to allopurinol would then require an alternative urate-lowering agent and the currently available option is febuxostat.

Febuxostat is a novel selective xanthine oxidase inhibitor that is used in lowering serum urate levels primarily in patients who are intolerant and non-responders to allopurinol. This drug received regulatory approval by the Ministry of Health (MOH) Malaysia in 2017. Before 2017, febuxostat use in Malaysian public hospitals required prior approval from the MOH. To date, there is limited data on febuxostat use in Malaysian gout patients. Hence, this study aims to describe our local

experience in terms of drug efficacy and safety using a new urate-lowering therapy, febuxostat.

Methods

This is a cross-sectional study conducted at the Rheumatology Clinic of Hospital Kuala Lumpur involving patients who received treatment from January 2013 to June 2018. Gout patients who required second-line urate-lowering therapy were included. Patients were not eligible if they had not previously used allopurinol as a first-line urate-lowering agent, had incomplete medical records, had coronary heart disease, or had chronic liver disease of Child-Pugh class C. Approval from the Medical Research Ethics Committee, Ministry of Health Malaysia was obtained and registration was completed in accordance with the National Medical Research Register Malaysia (NMRR-17-2273-37871).

The target sUA was <360 μmol/L. Management of hyperuricemia with urate-lowering therapy (ULT) was according to standard of care wherein febuxostat was initiated at 40 mg per day, and increased to 80 mg per day when target SUA was not attained.

The study had several objectives: examination of the proportion of gout patients who received febuxostat and achieved target sUA; assessment of the time taken to achieve target sUA; analysis of febuxostat dosage at achievement of target sUA; comparison of serum creatinine, estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease (MDRD) method,[9] and serum alanine aminotransferase (ALT) at baseline and at achievement of target sUA after febuxostat use.

Body mass index (BMI) according to the World Health Organization[10] classification was defined as the following: underweight corresponds to BMI of <18.5 kg/m^2, normal BMI value is between 18.5 to 24.9 kg/m^2, overweight is between 25.0 to 29.9 kg/m^2, and obese is ≥30.0 kg/m^2.

The current classification of chronic kidney disease (CKD) is based on the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline.[11] CKD is defined as structural or functional abnormalities of the kidney, present for ≥3 months, with or without decreased GFR, that can lead to decreased GFR; or eGFR <60 ml/min/1.73 m^2 that is present for ≥3 months, with or without evidence of kidney damage.

Categorical variables were reported as frequency and percentage, while continuous data were expressed as the mean (standard deviation, SD) or median (interquartile range, IQR). Levels of serum creatinine, eGFR and ALT between baseline and when target SUA was achieved were analyzed using independent t-test. Values of $p<0.05$ were considered to be statistically significant. Analyses were performed using SPSS version 20.0 (IBM SPSS Inc., Chicago, IL, USA).

Results

All gout patients who received febuxostat as a second-line urate-lowering agent were included in this study. Altogether there were 24 patients. Twenty-three patients had a history of hypersensitivity reaction to allopurinol, while one had inadequate response to allopurinol. Of the 24 patients who received febuxostat, three developed hypersensitivity reaction to febuxostat wherein they experienced generalized pruritic maculopapular rash. One patient underwent successful desensitization to febuxostat and continued to receive the drug. Therefore, final analysis was undertaken on 22 patients.

Mean age of patients was 62.7 (SD 13.3) years, and 16 (72.7%) were men. Sixteen (72.7%) patients were of Malay descent, five were Chinese and one was Indian. Mean age at the onset of gout was 48.5 (SD 15.1) years. The earliest age at the onset of gout was 21 years in men compared to women at 48 years. Median duration of gout was 10 with interquartile range (IQR) of 12.8 years. Mean baseline sUA concentration was 599.5 (SD 90.6) μmol/L.

Mean body mass index (BMI) of the patients was 26.8 (SD 3.5) kg/m^2. Six (27.3%) patients had normal BMI, 11 (50%) were overweight, and five (22.7%) were obese. Fifteen (68.2%) patients had CKD and all of them were in CKD stage 3 (**Table 1**).

With regard to the concomitant use of drugs that exerted contributory effects to hyperuricemia, two patients received hydrochlorothiazide for management of hypertension, one received frusemide for treatment of pulmonary arterial hypertension, and one patient who had renal transplant received cyclosporine.

Patient characteristics and comorbidities are depicted in **Table 1**.

Table 1. Baseline demographics, gout history and comorbidities of patients.

Characteristics	Patients (n=22)
Age, years	62.7 (13.3)[a]
BMI, kg/m^2	26.8 (3.5)[a]
Gender	
Men	16 (72.7%)
Women	6 (27.3%)
Ethnicity	
Malay	16 (72.7%)
Chinese	5 (22.7%)
Indian	1 (4.6%)
Duration with gout, years	10 (12.8)[b]
Earliest age at onset of gout, years	
Men	21
Women	48
Baseline sUA, µmol/L	599.5 (90.6)[a]
Duration of febuxostat use, months	33.5 (26.3)[b]
eGFR (MDRD), n(%)	
≥90 ml/min	1 (4.5%)
60-89 ml/min	6 (27.3%)
45-59 ml/min	9 (40.9%)
30-44 ml/min	6 (27.3%)
15-29 ml/min	0 (0%)
<15 ml/min	0 (0%)
Metabolic syndrome	
Hypertension	19 (86.4%)
Diabetes mellitus	7 (31.8%)
Dyslipidemia	14 (63.6%)
Family history of gout	5 (22.7%)
Smoking	5 (22.7%)
Alcohol use	2 (9.1%)
Clinical manifestations of gout	
Tophi	19 (86.4%)
Radiographic bone erosion	9 (40.9%)
Medullary nephrocalcinosis	5 (22.7%)
Urate nephrolithiasis or urolithiasis	0 (0%)

[a] mean (SD); [b] median (IQR)

Twenty (90.9%) of 22 patients achieved target SUA (**Table 2**). The two patients who did not achieve target sUA had CKD. One had CKD stage 3a while the other had stage 3b. Thirteen of the 15 patients with CKD achieved target sUA. Median duration to achieve target sUA was 5.5 (IQR 8.5) months. Eleven (50%) patients achieved target sUA within six months of commencing febuxostat. By 12 months, 16 (72.7%) patients managed to achieve target sUA.

Five (22.7%) patients achieved target sUA within one month of therapy. Eleven (50%) patients reached target sUA at 6 months, 72.7% at 12 months and 90.9% at the end of study period.

Patients who had not achieved target sUA by six months with febuxostat 40 mg per day had dose escalation to 80 mg per day. One patient was an exception as she was commenced on febuxostat 80 mg. Eight patients (36.4%) achieved target sUA with febuxostat 80 mg.

Table 1. Gout history, renal function and febuxostat dosages of all patients who tolerated febuxostat

Pt	Age (years)	Gender	Ethnic group	Duration of gout (years)	Age at onset of gout (years)	Baseline eGFR (MDRD) (ml/min/1.73m ^{2})	Baseline sUA (µmol/L)	sUA after treatment with febuxostat (µmol/L)	Duration to achieve sUA <360 µmol/L (months)	Febuxostat dose to achieve sUA <360 µmol/L (mg)
1	67	M	M	29	38	47	519	325	1	40
2	77	F	M	13	64	52	518	287	1	40
3	54	M	C	6	48	81	608	294	1	40
4	67	M	I	21	46	41	561	301	1	40
5	63	M	M	10	53	39	516	272	1	40
6	46	M	M	10	36	58	619	331	3	40
7	74	F	M	5	69	61	410	325	3	40
8	58	F	M	7	51	74	612	348	4	40
9	50	F	M	2	48	56	805	350	5	80
10	85	M	M	14	61	32	638	359	5	40
11	63	M	C	19	44	93	550	353	6	40
12	33	M	M	8	25	69	612	322	8	80
13	69	F	M	5	64	60	735	346	9	80
14	69	M	M	3	66	82	478	323	9	40
15	57	M	M	24	33	39	698	358	10	80
16	59	M	M	18	41	46	599	294	10	80
17	77	M	M	10	67	54	605	343	13	40
18	83	F	M	10	73	40	591	357	17	80
19	68	M	C	32	36	54	725	357	21	80
20	67	M	C	9	58	55	672	265	34	80
21	35	M	C	10	25	32	625	420	NA	NA
22	59	M	M	38	21	53	492	439	NA	NA

Pt: patient; Gender - M: male, F: female; Ethnic group – M: Malay, C: Chinese, I: Indian; sUA: serum uric acid; eGFR (MDRD): estimated glomerular filtration rate (modification of diet in renal disease); NA: not applicable

Among the 15 patients who had CKD, 13 (86.7%) achieved target sUA. Seven (53.8%) of the 13 patients achieved target sUA within six months of febuxostat treatment. Of note, four of them achieved target sUA by one month. Seven (53.8%) patients achieved target sUA with febuxostat 40 mg while the remaining six (46.2%) required febuxostat 80 mg.

In terms of drug safety, comparison of serum creatinine, eGFR (MDRD) and ALT was made at baseline and at achievement of target sUA. Analysis of this set of data did not show any significant difference ($p>0.05$). Given the median duration of febuxostat use was 33.5 (IQR 26.3) months, further analysis was undertaken with regard to the comparison of serum creatinine, eGFR (MDRD) and ALT at baseline, and at every subsequent 12 months. Evaluation of these patients at 12, 24, 36 and 48 months also did not demonstrate statistically significant changes ($p>0.05$) when compared to baseline values. None of the patients had deranged ALT values throughout the course of treatment with febuxostat.

Febuxostat was generally well tolerated. Majority of patients who were switched to febuxostat did not develop hypersensitivity reaction (23/24 were allergic to allopurinol, while 3/24 were allergic to febuxostat). No other adverse effects were reported. Nonetheless, two patients were advised to discontinue febuxostat at seven months and 48 months of treatment. One of them was diagnosed to have coronary heart disease from coronary angiography several months after commencement of febuxostat. Coronary angiography was carried out during her work-up for pulmonary arterial hypertension. The other patient was later found to have sonographically-confirmed liver cirrhosis given the history of chronic alcohol consumption.

Discussion

Even though allopurinol is recommended as the first-line ULT for the management of gout,[12] its use has occasionally been hampered by the development of adverse events, in particular, serious cutaneous adverse reactions in certain patients. Studies have shown that a significant proportion of gout patients have concomitant CKD,[13] which impacts the management of gout. Given the general

understanding that allopurinol requires dose adjustment according to creatinine clearance, coupled with the fact that the safest and most effective dosing of allopurinol is still debatable, it is not unexpected for patients with gout and CKD to be prescribed suboptimal doses of allopurinol.[14] This inevitably leads to failure in achieving target sUA, culminating in greater frequency of gout flares among CKD patients. With the advent of febuxostat, an alternative ULT can be offered to patients who are intolerant to, or have failed to respond to, allopurinol.

A vast majority of the patients in our cohort achieved target sUA, a finding which concurs with previous studies confirming the effectiveness of febuxostat.[16-18] The fact that five of the 22 patients in our cohort achieved target sUA within one month of febuxostat therapy and seven achieved target sUA by three months of therapy proved that febuxostat is indeed a potent ULT. In addition, 10 of the 11 patients who achieved target sUA within six months of febuxostat treatment were in fact receiving a lower dose of febuxostat at 40 mg per day. Among the CKD patients in our cohort, there was an almost equal proportion who responded to febuxostat 40 mg and 80 mg per day, respectively. This observation demonstrated that a lower dose of febuxostat can be effective in patients with CKD. Hence, it would be prudent to initiate febuxostat at 40 mg per day instead of 80 mg per day in patients with mild to moderate renal impairment. In the event the target sUA is not achieved by six months, febuxostat dose can be escalated to 80 mg per day. Interestingly, the authors would like to highlight that two patients (Patients 14 and 17 in **Table 2**) who received febuxostat 40 mg per day eventually achieved target sUA, albeit at 9 months and 13 months, respectively. The reason why both patients remained on febuxostat 40 mg per day without dose escalation was because they encountered logistics issues, rendering them unable to attend clinic appointments at earlier dates. Of note, the usual dosing regime for febuxostat is 40 mg per day with dose escalation to 80 mg after two to four weeks.

With regard to drug safety, there were no major adverse events reported in our cohort. Liver and renal functions of our cohort were not significantly affected throughout the course of febuxostat therapy. Nevertheless, we had to discontinue febuxostat in one patient when sonographically-evident liver cirrhosis was detected, given the fact that febuxostat is predominantly metabolised in the liver. We concluded that the aetiology of liver cirrhosis was most likely attributed to alcohol and not febuxostat, as that patient had a long-standing history of alcohol consumption.[19] Notwithstanding the fact that he had received febuxostat for 48 months, his ALT had remained within the normal range throughout this period. Upon further consideration, the decision to discontinue febuxostat may not be valid as our patient had chronic liver disease of Child-Pugh class A. According to Khosrawan et al,[20] the pharmacokinetics of febuxostat were unaffected in patients with mild-to-moderate hepatic impairment i.e. Child-Pugh classes A and B, thus suggesting that febuxostat is only contraindicated in Child-Pugh class C.

Another patient correspondingly had febuxostat terminated at the seventh month of therapy after she was diagnosed to have coronary heart disease in the course of investigation for pulmonary arterial hypertension. This decision was made based on the findings in the CARES (cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular morbidities) trial that demonstrated an adverse impact of febuxostat on all-cause mortality as well as cardiovascular mortality in gout patients with coexisting cardiovascular disease, although the mechanism underlying the mortality risk remains unclear.[21]

Despite the encouraging findings, this study has its limitations given the small sample size. Therefore, caution should be exercised in interpreting our findings as this study may be statistically underpowered. Given the fact that current gout guidelines recommend for febuxostat to be used as a second-line urate-lowering agent, it is not unexpected that this would be the limiting factor in determining the sample size. We anticipate readers might question why other trials involving febuxostat had enormous sample sizes while our sample size was substantially smaller. We would therefore like to remind readers that those trials were comparative trials using allopurinol vs febuxostat as first-line urate-lowering agents. The second limitation is that this research did not compare the urate-lowering effect, safety and tolerability of febuxostat with allopurinol.

Conclusion

Our study showed that a significant proportion of gout patients with CKD managed to achieve

target sUA with a lower dose of febuxostat at 40 mg per day. We suggest that this dose be maintained for up to six months in the event that target sUA has not been achieved before considering dose escalation.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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