A prospective cohort of gouty arthritis patients presenting with hyperuricemia and chronic kidney disease stage 3 and 4 for the safety, efficacy and renal effect of febuxostat at Changhai Hospital, Shanghai, China

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Abstract

Background: Hyperuricemia (HU) is a risk factor for the onset of Chronic Kidney Disease (CKD) and accumulating evidence significantly associates it with disease progression. A major challenge in treating hyperuricemia with traditional Urate-Lowering Drugs (ULDs) are the adverse effects associated with the accumulation of these drugs or their metabolites in CKD patients. Due to these unwanted effects, doses of ULDs are down-regulated to levels commensurate with the kidneys' ability to excrete their metabolites. This leads to suboptimal efficacy. Febuxostat, a selective Xanthine Oxidase (XO) inhibitor has demonstrated high efficacy in reducing Serum Uric Acid (SUA) levels and is well tolerated in mild kidney disease. However, its efficacy, safety and renal effects have not been studied in patients with advanced kidney disease, hyperuricemia and gout.

Objective: To evaluate the safety, efficacy and renal effects of febuxostat in patients with HU, gout and CKD stage 3 and 4.

Design: This was a 16-week prospective study, single-center, open-label, self-controlled trial.

Methods: Thirty five patients included received febuxostat 40mg/day. Changes in kidney function tests; SUA levels; liver function tests and full blood count were evaluated. Gout was diagnosed based on 2015 ACR/EULAR criteria, and GFR was estimated using the MDRD formula.

Results: Febuxostat decreased SUA levels to a target <360micromol/L for uncomplicated gout in 5 (36%), n=14, and SUA decreased to a target<300micromol/L for complicated gout in 5 (24%), n=21. Changes in eGFR and SUA were statistically significant, with p=0.001 for both at 95% confidence interval. Mean absolute eGFR from baseline to week 16 represented 9.04 ml/min (19.05%), and was attributed to febuxostat (R^2= 0.9556, 96%). Changes in LFTs and full blood count were insignificant. No drug- related AE were reported.

Conclusion: Febuxostat, as a ULD was safe and effective in controlling SUA levels in patients with gout, hyperuricemia and CKD stage 3 and 4. The drug also exerted renoprotective effects in this patient group. The reduction in SUA by febuxostat was associated with improvement in eGFR and overall kidney function, although a causal relationship wasn't evaluated in this study.

Key words: Chronic kidney disease, Febuxostat, Hyperuricemia, Uric acid, Safety, Efficacy, Renoprotective effects

Introduction

Hyperuricemia has been associated with adverse outcomes in CKD. Recently, evidence has accumulated showing that HU has a role in the pathogenesis of hypertension, metabolic syndrome, cardiovascular disease and the progression of CKD, indicating the necessity for treatment even in the absence of symptoms of gouty arthritis[1]. HU is well known to be even more prevalent in patients with CKD[2,3] and has been reported to be a risk factor for kidney dysfunction[4-6]. The mechanism underlying the progression of kidney dysfunction by activation of XO has also been reported by Liu *et al*[7]. Activation of XO increases Reactive Oxygen Species (ROS) production and oxidative stress, as well as Uric Acid (UA) production, and causes vascular damage and organ dysfunction. Indeed, ROS is known to inactivate Nitric Oxide (NO) production and activates Renin-Angiotensin System (RAS), resulting in endothelial dysfunction and/or tubular injuries [8,9]. Alternatively, UA salts activate inflammasomes, triggering inflammation and leading to the development of tubular injuries[10,11]. Antihyperuricemic XO inhibitors are believed to suppress renal dysfunction via oxidative stress reduction and suppression of endothelial dysfunction and tubular injuries[12].

The incidence and prevalence of gout and HU are increasing worldwide secondary to a multitude of factors,

especially changes in dietary intake and lifestyle in both developed and developing countries[13].

According to Saag and Choi[13], global prevalence rate of gout ranges between 2.6% and 36%. Prevalence of HU in mainland China is estimated at 13.3% (19.4% in men and 7.9% in women) and that of gout stands at 1.1%[14]. These estimates are similar to the United Kingdom and Germany where prevalence stands at 1.4%. In the European Union (EU), the statistics are somewhere between 0.9% and 2.5%[15] with a twofold preponderance towards men[16,17].

These figures are comparable to those observed in other developed countries, such as the United States where diagnosed gout cases have been estimated at 2.13%[18]. The authors[18] found males to be more than twice as susceptible to have gout as their female counterparts. Additionally, citizens older than 65 years were observed to have the highest estimated prevalence standing at 4.9% diagnosed gout cases.

Accumulating data support an increase in the prevalence of gout that is potentially attributable to recent shifts in diet and lifestyle, improved medical care, and increased longevity[13]. The authors[13] identify non-modifiable (age and sex) and modifiable (obesity, use of diuretics, high purine intake both in food and beverages) risk factors as major drivers of HU and gout. The disease burden of chronic gout is substantial, both in social and economic terms. Patients with acute gouty flares or chronic gout experience lower health-related quality of life due to pain, activity limitation, and disability[19,20]. Work-related activity and productivity are also negatively impacted in this population[21]. In addition, the small subset of patients suffering from chronic gout refractory to conventional therapy experience a disproportionally greater overall disease burden. Furthermore, gout usually exists with a multitude of comorbidities, not the least of which is CKD. This further compound the problem of treatment options[21]. HU is not only a risk factor for the onset of CKD[4], but it is also significantly associated with its progression[14] and it is more prevalent in patients with CKD[3]. The world over, CKD is estimated to affect between 11-14% of adults in industrialized countries[22,23].

A number of ULDs exist to manage HU. However, most of them are either used with caution or contraindicated altogether in CKD due to their untoward adverse effects[24]. Owing to this, doses of ULDs are downgraded, which leads to suboptimal efficacy[24]. Febuxostat has been shown to be highly efficacious in reducing SUA and is reported to be well tolerated in patients with mild-moderate kidney dysfunction[25]. However, very few studies have addressed the safety, efficacy and renal effects of febuxostat in subjects with a cocktail of hyperuricemia, gout and stages 3 and 4 CKD. This study has set out to evaluate the safety and efficacy of febuxostat at a dose of 40mg/ day in the management of HU in gouty arthritis patients with CKD stages 3 and 4.

Materials and methods

Study design: This study was a 16-week prospective, single-center, open-label, self- controlled trial to evaluate the safety, efficacy and renal effects of febuxostat in patients with HU, gout and CKD stage 3 and 4. HU was defined as SUA above 420umol/L, and CKD stage 3 as eGFR between 60 and 30ml/min/1.73m^2, while CKD stage 4 was eGFR below 30ml/min/1.73m^2. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) formula, and gout was diagnosed in a step-wise manner using the combined 2015 American College of Rheumatology/ European League Against Rheumatism (EULAR) collaborative initiative gout classification criteria[26]. The domains of this classification criterion included clinical, laboratory and imaging. The entry criterion, which formed the first step, required the occurrence of at least one episode of pain, swelling or tenderness of a peripheral joint or bursa. The second step sought the presence of Monosodium Urate Monohydrate (MSU) crystals in a symptomatic joint, bursa or in a tophus. The presence of MSU was diagnostic for gout and no further scoring was required. If sufficient criterion were not met, step 3 studied clinical considerations: under pattern of joint or bursa involvement during symptomatic episode, a score of 1 was assigned to ankle or mid-foot involvement (without involvement of the first metatarsophalangeal (MTP) joint), and 2 was for involvement of the first MTP joint as part of monoarticular or oligoarticular episode. Under characteristics of symptomatic episode, erythema overlying affected joint (either patient reported or physician observed), inability to bear touch or pressure to affected joint and great difficulty with walking or inability to use affected joint was assigned 1 score each.

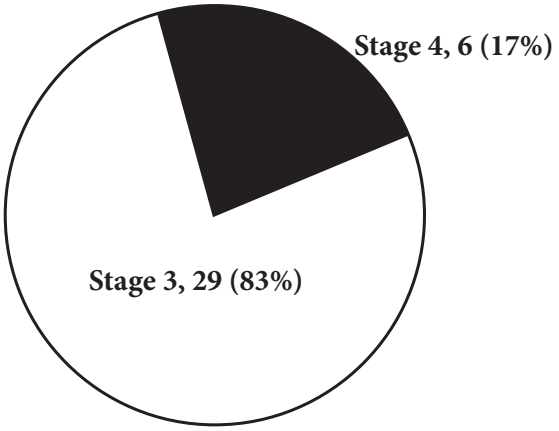
Study procedures: The first primary endpoint was the safety and tolerability of febuxostat. All suspected relationship between AEs and adverse reactions and the study drug was reported by the primary attending physician and evaluated based on the clinical course for AEs (timing of the event and reversal of event by cessation of the medication) and laboratory changes for the adverse reactions. 'Possibly' indicated that, although a relationship between the AE and the study drug could not be excluded, the probability that they were connected was considered to be fairly low. 'Probably' indicated that the probability that AE and the study drug were related and considered to be relatively high. The second primary end point included relative (%) change from baseline of SUA. The first secondary endpoint comprised of the achievement rate of the target SUA of 360 umol/L for uncomplicated gout and 300umol/L for complicated disease. Complicated gout is tophiceous gout or the presence of nephrolithiasis (as guided by the 2016 EULAR evidence-based recommendations for the management of gout)[5]. The final secondary endpoint studied the relative (%) changes in eGFR at 16 weeks from their baseline levels.

Data analysis: Statistical packages used for data analysis were SPSS (version 22, IBM 2013, USA) and MS Excel using the following methods therein: Descriptive statistics - measures of central tendency and dispersion were used to report the findings on the demographics and other study parameters. Inferential Statistics – the student t-test (Wilcoxon) and comparison of two means were used to test the hypothesis and ascertain general associations between various variables.

Results

Description of patients according to stage of renal failure: One hundred percent of the patients under study (n=35) had either stage 3 or stage 4 CKD. Twenty nine patients, representing 83% had stage 3 renal failure, and 6 (17%) patients had stage 4. Figure 1 depicts a graphical representation of patient distribution. All the study participants (n=35) were on febuxostat 40 mg once daily.

Figure 1: Patient distribution according to stage of renal failure

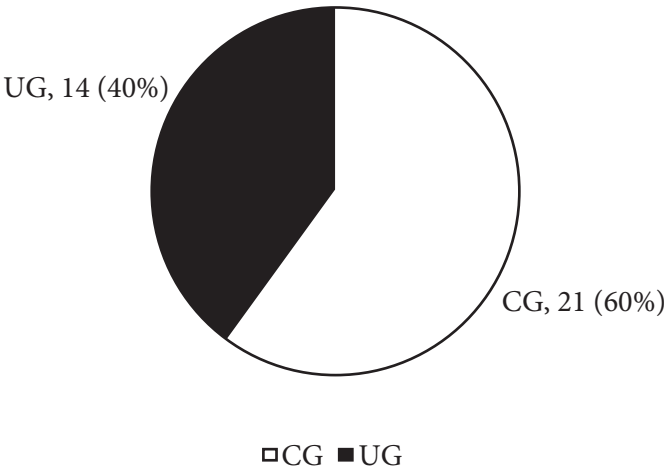


Presence of nephrolithiasis and tophi (complicated gout): Of the 35 patients studied, 35 patients, representing 100% had history of tophi and/or nephrolithiasis recorded. Out of these patients, 21, representing 60% had a history of nephrolithiasis and/or tophi (complicated gout) (Table 1, Figure 2), and 14 patients, representing 40% did not.

Table 1: Patient history of nephrolithiasis/tophi

Characteristics	Frequency	(%)
No	14	40
Yes	21	60

Figure 2: Patient distribution into complicated and uncomplicated gout



UG= Uncomplicated Gout; CG= Complicated Gout

Renal function parameters: Table 2 displays data on the renal functions using standard parameters of measurement. Foremost, descriptive statistics and trend line analysis has been done for the parameters of renal function for the period of 5 months. During a period of 5 months of assessment of patients on febuxostat, results on renal function were recorded. The parameters used to assess renal function were serum creatinine, BUN, UA and eGFR. For the purposes of the paired sampled t-test used, the month 1 was the baseline or the pre-test result and month 5 as the outcome or post-test after febuxostat treatment. Therefore, the descriptive statistics for each parameter are for month 1 and month 5.

Table 2: Descriptive statistics of renal parameters

Statistics			95% Confidence Interval
Mean	Serum creatinine(umol/L) at month 1	141.869	131.376 - 152.802
	Serum creatinine(umol/L) at week 5	125.923	111.444 - 143.787
	BUN (mmol/L) at month 1	9.4783	8.0175 - 10.8848
	BUN (mmol/L) at month 5	9.6289	7.9109 - 11.6472
	Uric acid (umol/L) at month 1	610.557	566.461 - 650.216
	Uric acid (umol/L) at month 5	347.266	327.634 - 368.859
	eGFR (ml/min) at month 1	47.4546	43.1637 - 51.6152
	eGFR (ml/min) at month 5	56.4886	50.0713 - 63.1101
Median	Serum creatinine (umol/L) at week 1	135.000	125.000 - 141.000
	Serum creatinine (umol/L) at week 5	113.000	105.000 - 127.000
	BUN (mmol/L) at month 1	8.3000	7.5000 - 10.0000
	BUN (mmol/L) at month 5	8.1000	7.3300 - 8.9000
	Uric acid (umol/L) at month 1	610.000	560.000 - 683.644
	Uric acid (umol/L) at month 5	340.000	310.000 - 364.000
	eGFR (ml/min) at month 1	50.7375	41.5642 - 54.9400
	eGFR (ml/min) at month 5	55.1867	49.4811 - 65.8852
Std. Deviation	Serum creatinine (umol/L) at week 1	34.2355	23.5661 - 43.0866
	Serum creatinine (umol/L) at week 5	48.6479	24.7631 - 69.2266
	BUN (mmol/L) at month 1	4.29422	2.91041 - 5.21149
	BUN (mmol/L) at month 5	5.64731	2.47575 - 7.82762
	Uric acid (umol/L) at month 1	129.6423	101.5358 - 154.1640
	Uric acid (umol/L) at month 5	61.2968	41.6308 - 77.9505
	eGFR (ml/min) at month 1	12.85501	9.33068 - 16.07469
	eGFR (ml/min) at month 5	19.77694	14.59987 - 24.08033

Renal function results: Table 3 shows a paired sampled t-test for renal function results of 1 month and 5 month categories.

Table 3: Renal function results

Paired samples T-test (n=35)								
Parameter		Paired Differences			95% Confidence	t	DF	P-value
		Mean difference	Std. Deviation	Std. Error Mean	Interval of the Difference			
Serum Creatinine	Srmcrtmonth1 Srmcrtmonth5	15.9457	32.3550	5.4690	4.8314 -27.0600	2.916	34	0.006
BUN	Bunmonth1bunmonth5	-0.15057	4.01324	0.67836	-1.52917- 1.22803	-0.222	34	0.826
Uric Acid	Urratemonth1 Urratemonth5	263.291429	118.8772	20.0939	222.4557 - 304.1272	13.103	34	0.001
eGFR	Egfrmonth1egfrmonth5	9.03394	11.28210	1.90702	5.15841 – 12.90948	4.737	34	0.001

Change in eGFR results over the study period (month 1 to month 5): The change in eGFR for all the patients (n= 35) was studied and recorded. Figure 3a and 3b show the absolute figures of the change in eGFR from month 1 to month 5.

Figure 3a: Changes in eGFR for 18 patients (from 1 to 18)

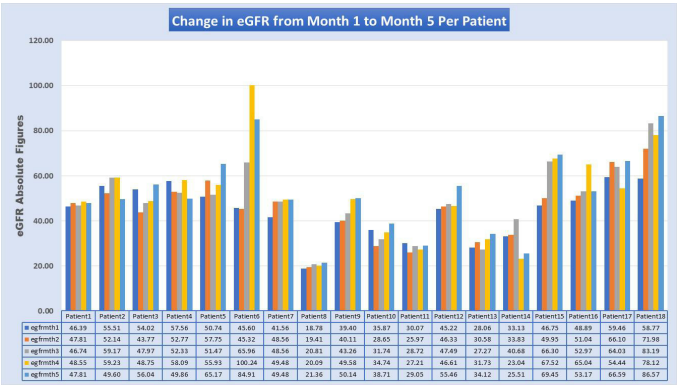
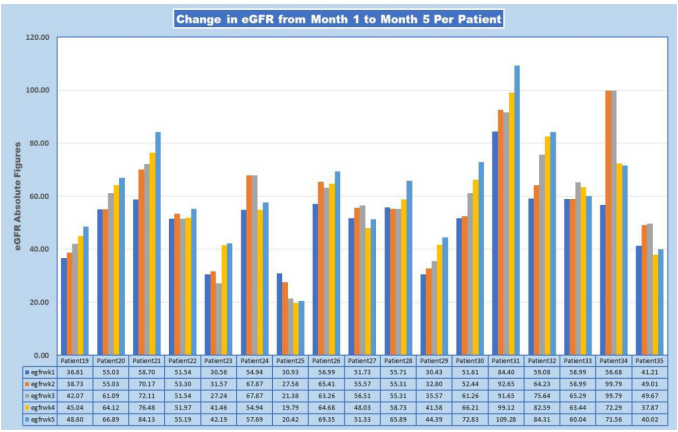


Figure 3b: Changes in eGFR for 17 individual patients (from 19 to 35)



Summary of changes in eGFR for 35 patients: To summarise the change in eGFR, Figure 4a depicts a graphical representation of the mean change every month for 5 months. The R^2 shown (0.9556) in the graph below indicates that 96% of changes in eGFR in patients across the period of 5 month is explained by the treatment given to the patients. Figure 4b shows this change in percentage form. The R^2 shown (0.9568) in the graph means that 96% of changes in eGFR in patients over the 5 month-period can be attributed to the febuxostat administered to the patients.

Figure 4a: Mean changes in eGFR for all the patients (n = 35)

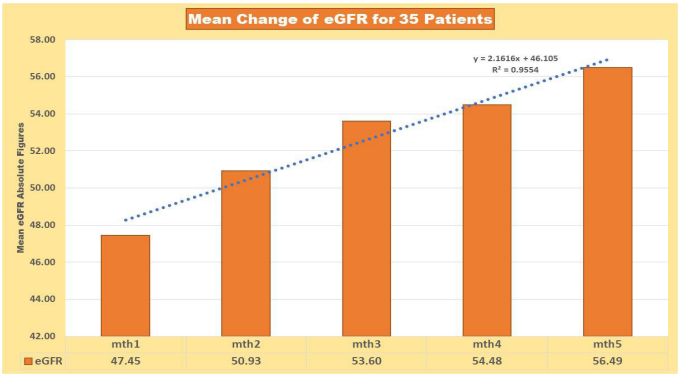
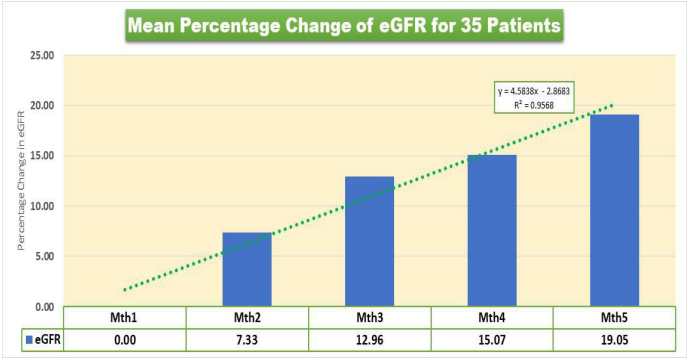


Figure 4b: Percentage change in eGFR for all the patients (n=35)



Full blood count results – Paired sample t-test test statistics: Using the paired sampled t-test. Table 4 shows the statistics test result of the named parameters.

Table 4: Full blood count results

Paired samples T-test (n=35)								
Parameter		Paired Differences			95% Confidence	t	df	P-value
		Mean difference	Std. Deviation	Std. Error Mean	Interval of the Difference			
WBC	Wbcmth1 Wbcmth5	-0.10667	1.82604	0.43040	-1.01474 – 0.80140	-0.248	17	0.807
RBC	rbcmonth1 rbcmonth5	-0.07643	0.37932	0.10138	-0.29544 – 0.14259	-0.754	17	0.464
Haemoglobin	hemmonth1 hemmonth5	-6.1111	13.9743	3.2938	-13.0604 – 0.8381	-1.855	17	0.081
PLT count	ptlcmonth1 ptlcmonth5	1.5000	52.3419	12.3371	-24.5290 – 27.5290	0.122	17	0.905

Liver function test statistics results: Using paired sampled t-test statistic, the following are the results for the parameters used in the study.

Table 5: Liver function results

Paired samples T-test (n=35)								
Parameter		Paired Differences			95% Confidence	t	df	P-value
		Mean difference	Std. Deviation	Std. Error Mean	Interval of the Difference			
ALT	Altcmonth1 altmonth5	-4.6000	17.9250	4.0081	-12.9892 – 3.7892	-1.148	19	0.265
AST	astmonth1 ast-month5	-4.4000	15.6555	3.5007	-11.7270 – 2.9270	-1.257	19	0.224
TB	tbmonth1 tb-month5	-1.5444	6.5998	1.5485	-4.8115 – 1.7227	-0.997	17	0.333
TP	tpmonth1 tp-month5	-1.5400	7.7723	3.4759	-11.9905 – 8.1105	0.443	4	0.681
ALB	Albmonth1 Alb-month5	0.7200	3.9865	1.7828	-4.2299 – 5.6699	0.404	4	0.707
ALP	Alpmonth1 Alpmonth5	-31.4000	34.1585	15.2761	-73.8133 – 11.0133	-2.055	4	0.109
LDH	Ldhmonth1 Ldhmonth5	5.8000	65.7548	29.4665	-75.8454 – 89.4454	0.197	4	0.853

Discussion

This study had three findings. We demonstrated that febuxostat was safe and tolerable in patients with stages 3 and 4 CKD; we showed that the drug was efficacious in reducing SUA levels in this patient group, and we proved that febuxostat possesses renoprotective effects by not only halting the process of renal dysfunction, but also reversing kidney injury and improving renal function indicators, such as eGFR.

Up until febuxostat was approved for use in HU and gout, there were several attempts at controlling SUA levels using ULD, like allopurinol in patients with CKD. These attempts proved futile for various reasons: Firstly, allopurinol, another XO inhibitor, is excreted in urine, and its serum concentration and AE increase in patients with CKD, requiring dose adjustments from early stages of CKD and resulting in poor control of SUA levels[12]. Secondly, Paisansinsup *et al*[27] report the rate of possible or definite AEs of allopurinol in CKD to range from 10.5% to 13.9% depending of the stage of CKD. Our study demonstrated that these statistics are much worse than the safety profile of febuxostat. Thirdly, the active metabolite of allopurinol, oxypurinol, which is associated with AE, is increased in patients with CKD[12]. Finally, Yamaguchi *et al*[12] reported several studies that have indicated severe Allopurinol Hypersensitivity Syndrome (AHS) in patients with CKD that could prove fatal. This syndrome has not been reported to occur with febuxostat, and our study recorded no cases related to hypersensitivity syndrome.

Becker *et al*[28] assert that although incidence is low and severity is mild-moderate, headache, dizziness, diarrhoea, nausea, rash, cramps and twitches (muscle-related adverse effects) and liver function abnormalities are AE frequently observed with febuxostat. Our study didn't record any patient- reported AE, and the analysis of liver function tests at baseline and at week 16 was statistically insignificant. Additionally, the increased rate of flares associated with febuxostat initiation were not observed in this current study since flare prophylaxis was

initiated concurrently with febuxostat according to a study by Khanna *et al*[29].

Schumacher *et al*[30] and Becker *et al*[28] raised concerns about increased cardiovascular events (non-fetal MI, non-fetal stroke and cardiovascular death) to the risk of events associated with febuxostat. For these events to likely occur, the patients should have a history of cardiovascular disease and/or risk factors for developing cardiovascular disease[30]. White *et al*[31] reported a higher risk of adverse cardiovascular events associated with febuxostat more than allopurinol. However, it can't be ascertained if these cardiovascular events could purely be attributed to febuxostat, or if there is a role of underlying HU which is in itself a risk factor for cardiovascular disease[32,33]. Although baseline CVS investigations such as echocardiogram were outside the scope of this study, we didn't record worsening cardiovascular status in patients with existing CVD, and we did not observe any new CVS pathology that we could tie to febuxostat.

Our study showed no evidence of haematologic abnormalities contrary to reports in the WHO newsletter[34] of 13 patients with agranulocytosis, and Kabayashi *et al*[35] who reported cases of acute neutropenia associated with febuxostat in patients with CKD. Although Choham[36] reported early severe immunological reactions like Stevens-Johnson syndrome (SJS) in patients taking febuxostat, the majority of these patients with immunological reactions also had a history of allopurinol hypersensitivity and/or renal impairment. Therefore, it is inconclusive if these reactions could purely be attributed to febuxostat. Our study recorded no cases of immunological reactions.

Several reasons have been advanced to support the impressive safety profile of febuxostat as compared to other ULDs. Firstly, febuxostat is primarily metabolized in the liver[12]; secondly, the drug is 49.1% excreted in urine and 44.9% through faeces[37]. Therefore, febuxostat possesses strong anti-hyperuricemic effect without serious AE even in patients with CKD without dose adjustments[38,39]. Thirdly, febuxostat is highly selective in its mechanism of action, and finally, the drug is not uricosuric and thus, is less likely to cause urolithiasis[37].

Hosoya and Ohno[40] studied pharmacokinetic and pharmacodynamic properties of febuxostat in patients with mild-to moderate kidney failure. They reported that although renal dysfunction caused an increase in systemic exposure to unchanged febuxostat, the noted increase was slight in patients with mild-to-moderate renal dysfunction. No AEs were observed, and unchanged febuxostat or its metabolites did not accumulate after repeated exposure[40]. Although our study did not collect and analyse pharmacokinetic and pharmacodynamic data, it can be assumed with confidence that the safety and tolerability of febuxostat is high even in the presence of advanced CKD.

The percentage of patients on febuxostat constant dose of 40mg/day who achieved target SUA levels of 360micromol/L or less for uncomplicated gout, as recommended by the 2016 EULAR evidence-based recommendations for the management of gout[15], was 36%, and those that reached SUA of 300micromol/L or less for complicated gout were 24%. A large study with longer follow-up time which addressed febuxostat efficacy in patients with moderate-to-severe renal dysfunction found febuxostat to reduce SUA levels to 360micromol/L in 44%, 46% and 60% of patients with mild renal dysfunction who were taking 80, 120, and 240mg/day of febuxostat, respectively[38]. Becker *et al*[39] reported that patients with CKD stage 3 on 40 and 80mg/day of febuxostat achieved SUA levels 360 micromol/L in 43.1% and 71.3% of cases, respectively. From the foregoing, 80 mg/day of febuxostat reduced SUA to 44% in mild CKD, and 40mg/day of febuxostat reduced SUA levels below 360 micromol/L in 43.1% in CKD stage 3. Our study evaluated patients with moderate-to-severe CKD with uncomplicated and complicated gout, while applying stringent SUA levels of below 300micromol/L for complicated gout. Additionally, febuxostat dose was kept at 40mg/day throughout the study period of 16 weeks. Although previous studies[39,38] have shown better efficacy at higher doses of febuxostat, our study was limited to 40mg/day due to cost constraints.

Our study found that febuxostat was efficacious in reducing SUA levels in patients with advanced renal dysfunction and complicated or uncomplicated gout. Before the advent of febuxostat, allopurinol was the only available ULD, but its dose needed downward adjustment to levels commensurate with the kidneys' ability to excrete its metabolites[12]. Furthermore, the efficacy of allopurinol is much less than that of febuxostat, more so with the reduced doses permissible in patients with kidney failure[39]. Nakaya *et al*[24] reported that in Japan physicians limit the dose of allopurinol to only 100mg/day in CKD stages 4 and 5, rendering its use as ULD in this patient group ineffective.

Iseki *et al*[4] and Koratala *et al*[6] have demonstrated that HU is a risk factor for the progression of kidney dysfunction in the general population and CKD patients. As a result, ULDs are expected to contribute to renal protection. Additionally, Becker *et al*[41] reported that in patients with either mild or no renal dysfunction, taking 40–120mg of febuxostat/day for 5 years improves eGFR by 1ml/min from baseline for every 60 micromol/L decrease in SUA.

In this study, we showed that lowering SUA resulted in improved eGFR in CKD patients, with an absolute mean improvement in eGFR from baseline to week 16 of 9.04 ml/min and a mean percentage change of 19.05%. Although we didn't evaluate the direct relationship between absolute change in SUA and absolute change in eGFR, our findings support the hypothesis postulated by Goicoechea *et al* [42] and Sircar *et al*[43] that lowering SUA levels by ULDs in patients with CKD ameliorates eGFR reduction, and is therefore, renoprotective. Whereas Levy *et al*[44] reported that renal dysfunction could be suppressed with ULDs in patients with controlled SUA levels at <360micromol/L, our study found that deterioration of kidney function could be suppressed in patients with SUA

levels controlled more strictly in patients with complicated gout.

The mechanism by which febuxostat is renoprotective is not well understood, although several theories have been advanced. Johnson *et al*[45] suggests that ULDs block RAS, resulting in a decrease in glomerular hypertension, which in turn preserves GFR. Additionally, the authors assert that ULDs confer a renoprotective effect by suppressing uric acid's oxidative stress on the endothelium.

HU and XO activation are vascular injury factors. XO activation increases oxidative stress, suppresses NO production, and activates RAS[9,46]. Sánchez-Lozada *et al*[46] reported that HU induces arteriolopathy of pre-glomerular vessels, impairing endothelial function and the autoregulatory response of afferent arterioles, resulting in glomerular hypertension. ULD, febuxostat is thought to improve these vascular events by inhibiting XO and suppressing HU.

Conclusion

Febuxostat, as a ULD was safe and effective in controlling SUA levels in patients with gout, HU and CKD stage 3 and 4. The drug also exerted renoprotective effects in this patient group. The reduction in SUA by febuxostat was associated with improvement in eGFR and overall kidney function, although a causal relationship was not evaluated in this study.

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