

Switching from Allopurinol to Febuxostat: A Comparison of The Rate of Renal Functional Decline in Patients With Moderate and Severe Chronic Kidney Disease



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Abstract

Allopurinol has been widely used as a urate-lowering agent in the treatment of hyperuricemia. However, patients with renal impairment require dose reduction according to their renal function. On the other hand, strict dose adjustment is not required for the use of febuxostat and the frequency of its use is increasing. The purpose of this study was to clarify the effects of the rate of renal functional decline and other examination data by switching from allopurinol to febuxostat in patients with moderate to severe renal dysfunction. We examined the clinical records of patients treated at the Saga University Faculty of Medicine, Department of Nephrology between March 2008 and December 2016; patients who received orally-administered allopurinol for more than one year and who were able to change to febuxostat and were followed for more than two years were analyzed. The patients were divided into 3 groups: CKD(Chronic kidney disease) stage 3 (n = 12), CKD stage 4 (n = 10), and CKD stage 3 and 4 combined (n = 22), according to the renal function at the time of switching to febuxostat. There was no significant difference in the rate of renal functional decline (Δ eGFR: Δ estimated glomerular filtration rate) in any group; however, the rate after the switch tended to be decreased in comparison to before the switch.

Keywords: Febuxostat; Allopurinol; Hyperuricemia; Chronic Kidney Disease

Abbreviations: CKD: Chronic Kidney Disease; XO: Xanthine Oxidase; Cr: Creatinine, eGFR: Estimate Glomerular Filtration Rate; BUN: Blood Urea Nitrogen; UA: Uric Acid; TP: Total Protein; Alb: Albumin; Hb: Hemoglobin; TC: Total Cholesterol; TG: Triglyceride; UP/UCr: Urinary Protein / Urine Creatinine Ratio

Background

Hyperuricemia has been reported to be related to the rapid progression of the renal functional decline in patients with chronic kidney disease (CKD) [1]. Furthermore, hyperuricemia is one of the causes of gout and kidney stone disease, and lifestyle diseases that cause cardiovascular disease, cerebrovascular disease, and arteriosclerosis. Allopurinol has been widely used as urate-lowering agent in the treatment of hyperuricemia. Allopurinol reduces the uric acid concentration by acting as a xanthine oxidase (XO) inhibitor. Allopurinol is metabolized by XO and aldehyde oxidase and to oxypurinol, which is also a XO inhibitor. Oxypurinol is predominantly excreted by the kidney; thus, the risk of adverse events is higher in CKD patients. febuxostat is a novel XO inhibitor that became clinically available in Japan in 2011. Although it was reported that febuxostat was safe and effective in patients

with moderate to severe kidney dysfunction [2], few studies have examined the usefulness of switching from allopurinol to febuxostat in advanced CKD patients. The aim of the present study was to clarify the effects of the rate of renal functional decline and other factors in patients with moderate to severe renal dysfunction who switched from allopurinol to febuxostat.

Patients & Methods

We examined the clinical records of patients who were treated in the Department of Nephrology, Saga University Faculty of Medicine from March 2008 to December 2016. Patients who received orally-administered allopurinol for more than one year and who were able to change to febuxostat and who were followed for more than two years were analyzed. The doses of allopurinol

before switching and the dosage of febuxostat after switching were not defined. Patients with mild renal dysfunction (CKD stage 1 or 2) and those with end-stage renal failure (CKD stage 5) were excluded. The patients (n=22) were divided into three groups according to their renal function when they switched to febuxostat: the CKD stage 3 group (S3, eGFR 30 ml/min/1.73m² to 60 ml/min/1.73m²; n = 12), CKD stage 4 group (S4, eGFR 15ml/min/1.73m² to 30 ml/min/1.73m²; n = 10), CKD stage 3 and stage 4 combined group (S3+4). The primary outcome was the annual rate of change in the eGFR (Δ eGFR). The Wilcoxon signed rank sum test was used to compare the data before and after switching from allopurinol. P values of <0.05 were considered to indicate a significant difference. All statistical analyses were performed using the JMP Pro 12 software program.

Result

The average age of the patients in the S3 group was 53 ± 13 years, and the average age of the patients in the S4 group was 69±

10 years. The patients in the S4 group were older than those in the S3 group. A male predominance was observed in both the S3 and S4 groups; the male to female ratio was 11:1 in the S3 group. Furthermore, the proportion of chronic glomerular nephritis as an underlying disease was high in both the S3 and S4 groups. In addition, the rate of nephrotic syndrome was high in the S3 group, while the rate of diabetic nephropathy was high in the S4 group. The average eGFR in the S3 was 41.5 ± 7.63 ml/min, while that in the S4 group was 21.3 ± 3.84 ml/min. The average eGFR in the S3+4 group was 32.3 ± 11.81 ml/min (Table 1). The annual rates of change in the eGFR (Δ eGFR) of the S3 group in the year before switching from allopurinol to febuxostat, at one and two years after the switch are shown in Figure 1A. The Δ eGFR indicates that the rate of renal functional decline was faster when the value was low. There was no significant difference after 1 year, 2 years after switching compared with before switching. We focused on the average value (Figure1B). The Δ eGFR was -1.66 ml/min/1.73 m²/year before the change to febuxostat.

Table 1: Characteristics of each groups. At switching from allopurinol to febuxostat.

	Stage 3 (n=12)	Stage 4 (n=10)	Stage 3+4 (n=22)
Sex (M : F)	11:01	06:04	17:05
Age (years)	57 ± 13	69 ± 10	63 ± 13
Primary disease (%)			
Diabetic nephropathy	0	20	9.1
Nephrosclerosis	0	10	4.5
Chronic glomerulonephritis	41.6	50	45.5
Nephrotic syndrome	41.6	0	22.7
Others	16.6	20	18.2
Cr (mg/dl)	1.4 ± 0.26	2.3 ± 0.32	1.8 ± 0.51
eGFR (ml/min)	41.5 ± 7.63	21.3 ± 3.84	32.3 ± 11.81
BUN (mg/dl)	23.4 ± 7.58	41.8 ± 19.24	31.7 ± 16.83
UA (mg/dl)	7.5 ± 0.85	7.9 ± 1.29	7.7 ± 1.09
TP (g/dl)	7.2 ± 0.52	7.1 ± 0.64	7.1 ± 0.58
Alb (g/dl)	3.9 ± 0.48	3.7 ± 0.45	3.8 ± 0.48
Hb (g/dl)	13.2 ± 2.53	11.7 ± 1.72	12.6 ± 2.34
TC (mg/dl)	194.4 ± 38.78	(n=9) 198.2 ± 27.84	(n=21) 196.1 ± 34.3
TG (mg/dl)	173.9 ± 69.02	(n=8) 155.8 ± 85.48	(n=20) 166.1 ± 77.04
UP/Ucr (g/gCr)	0.6 ± 0.66	(n=9) 1.1 ± 1.2	(n=21) 0.8 ± 0.97

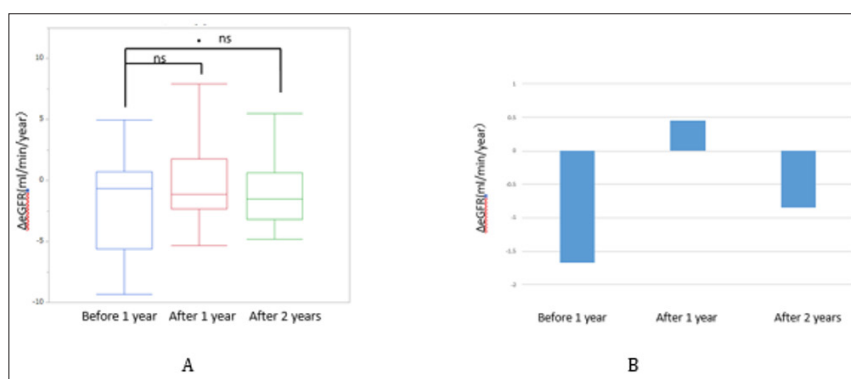


Figure 1: A: Δ eGFR (ml/min/year) of S3 group, B: Δ eGFR (ml/min/year) of S3 group(average).

In contrast, the Δ eGFR was 0.45 ml/min/1.73 m²/year after one year switching to febuxostat and the Δ eGFR was -0.8 ml/min/1.73 m²/year in the two years after the switch; thus, the rate renal functional tended to decrease. The Δ eGFR in the S4 group during the year before switching from allopurinol to febuxostat, and at one and two years after the switch are shown in Figure 2A. There was no significant difference after 1 year and 2 years after switching compared with before switching. Regarding average value, the Δ eGFR before the switch was -1.71 ml/min/year. The Δ eGFR values

at one and two years after the switch were -1.36 ml/min/year and -1.59 ml/min/1.73 m²/year, respectively (Figure 2B). Although there was no significant difference, the rate of renal functional decline after switching tended to be slower in comparison to before switching. The Δ eGFR values of the S3+4 group are shown in Figure 3A. There was no significant difference after 1 year and 2 years after switching compared with before switching. Regarding average value, the Δ eGFR before the switch was -1.69 ml/min/1.73 m²/year.

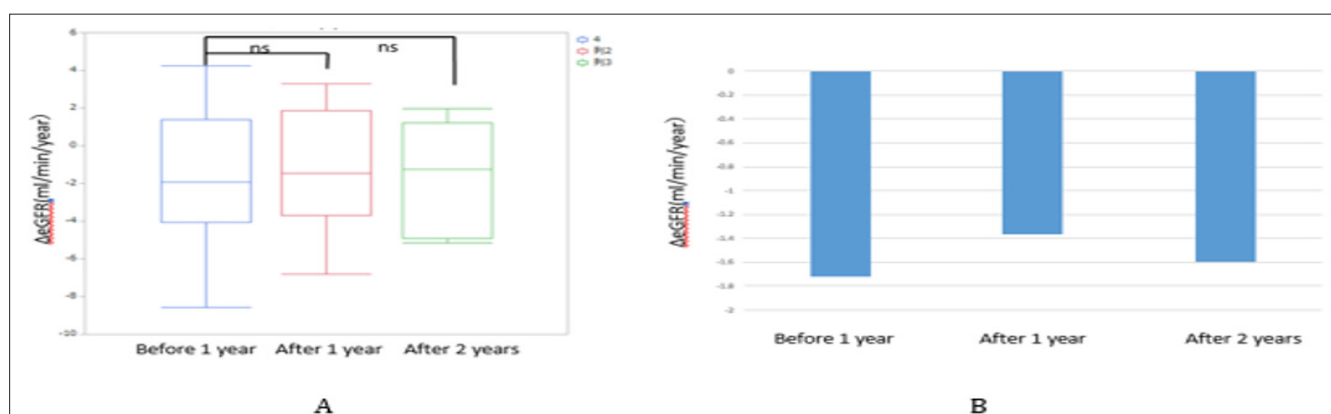


Figure 2: A: Δ eGFR (ml/min/year) of S4 group, B: Δ eGFR (ml/min/year) of S4 group(average).

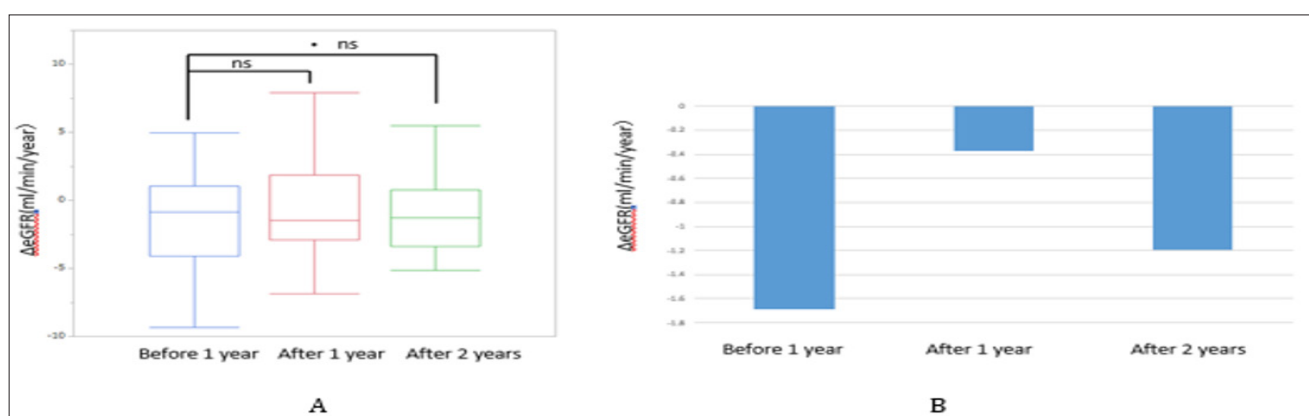


Figure 3: A: Δ eGFR (ml/min/year) of S3+4 group, B: Δ eGFR (ml/min/year) of S3+4 group(average).

The Δ eGFR values at one and two years after the switch were -0.37 ml/min/1.73 m²/year and -1.19 ml/min/1.73 m²/year, respectively. There was no significant difference in the combined group; however, the rate of renal functional decline tended to decrease after the switch. The clinical laboratory data that showed significant changes during the observation period are shown in (Table 2). The uric acid value at two years after the switch was significantly reduced in comparison to before the switch in the S4 and S3+4 groups (Figure 3B). In addition, the total protein level was significantly decreased in the S3 and S3+4 groups. There were no obvious adverse events during the two years of febuxostat treatment.

Discussion

Goicoechea et al. [3] conducted a prospective, randomized trial of 113 patients with an estimated GFR (eGFR) value of <60 ml/min. Patients were randomly assigned to treatment with allopurinol 100 mg/day (n = 57) or to continue the usual therapy (n = 56). The eGFR increased to 1.3 mL/min/1.73 m² in the allopurinol group, whereas it decreased to 3.3 mL/min/1.73 m² in the control group, and a significant difference was found between the two groups. The serum uric acid concentration reportedly decreased by 1.8 mg/dL in the allopurinol group and increased by 0.2 mg/dL in the control group. Based on the results shown in Figures 1-3, although the difference was not statistically significant, the Δ eGFR

after switching to febuxostat was lower in comparison to before the switch. As shown in (Table 2), the uric acid level was significantly decreased. It was suggested that a decrease in the serum uric acid value may slow the rate of renal functional decline. Dipankar et al.

Table 2: Data with significant difference.

	S3	S4	S3+S4
UA (mg/dl)		7.60→6.95 (after 2years) p=0.0366	7.60→6.75 (after 2years) p=0.0010
TP (g/dl)	7.45→7.05 (after 1year) p=0.0078 7.45→7.15 (after 2years) p=0.0352		7.25→7.00 (after 1year) p=0.0350

The proportion in the placebo group was 54%, while that in the febuxostat group was 38%. It was reported that febuxostat might slow the decrease in the eGFR. Furthermore, Tsuruta et al. [5], performed a 1-year cohort study of 73 hyperuricemic patients with an eGFR of <45 ml/min who were treated with allopurinol as urate-lowering therapy. In 51 patients, the treatment was changed from allopurinol to febuxostat; the other 22 patients continued to receive allopurinol. The eGFR decreased from 27.3 to 25.7 ml/min in the febuxostat group and from 26.1 to 19.9 ml/min in the allopurinol group. These reports support the possibility that switching from allopurinol to febuxostat might have reduced the rate of renal functional decline in the present study. In this study, the switching from allopurinol to febuxostat reduced the serum uric acid concentration but was not found to lead to a decrease in the urine protein excretion. However, the amount of urinary protein may be due to the result of the decreased renal function. Furthermore, the amount of total protein after the change to febuxostat was significantly decreased in the S3 and S3 + 4 groups, but not in the S4 group. Since the incidence of nephrotic syndrome in the S3 group was higher than that in the S4 group, the progression of nephrotic syndrome might have influenced the amount of total protein.

Schumacher HR Jr et al. [6] reported that the rates of adverse event rates 1072 hyperuricemic patients who received febuxostat, allopurinol, or a placebo for 28 weeks were similar. In this study, no patients experienced adverse events after switching to febuxostat [6]. If febuxostat is superior to allopurinol with regard to slowing the rate of renal functional decline, then it would seem appropriate for patients to switch from allopurinol to febuxostat.

Conclusion

In patients with moderate and severe CKD, switching from allopurinol to febuxostat may reduce the rate of renal functional

[4]. compared patients who were treated with febuxostat to those who received a placebo over a 6-month period in 93 patients with stage 3 or 4 CKD. The primary outcome was the proportion of patients that showed a >10% decline in their eGFR.

decline. A large-scale study with long-term observation should be performed in the future.

Conflict of Interest

The authors have no conflicts of interest directly relevant to the content of this article.

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