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Efficiency of febuxostat (Adenuric®) in preventing of further GFR decline in patients with hyperuricemia with and without diabetic nephropathy associated and chronic kidney disease

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Abstract

Objectives. To assess the efficiency of Febuxostat in preventing of further GFR decline in patients with hyperuricemia with and without diabetic nephropathy (DN) associated and chronic kidney disease (CKD). Material and methods. The prospective study enrolled 73 adult patients with hyperuricemia and CKD of 3A-4 stages (34 patients with DN and 39 without DN). In all cases, baseline and 6 months after beginning of the treatment uric acid serum levels, estimated glomerular filtration rate (eGFR). All patients with DN were randomized into two groups: treatment with febuxostat 40 mg daily (n=16) or placebo (n=18). Patients without DN were similarly randomized: treatment with the same dose of febuxostat (n=20) or placebo (n=19). Statistical significance was considered when P value was <0.05. Results. In patients with DN who received febuxostat or placebo and in patients without DN who received febuxostat or placebo mean baseline eGFR showed no difference (p>0.05). Six months after treatment with febuxostat, eGFR in patients with and without DN changed insignificantly and was 41.63±3.48 and 41.3±7.92 respectively (p>0.05). In patients with and without DN, who received placebo, there was a significant decrease in mean eGFR six months after the treatment: 24.0± 6.51 and 33.26±4.78 correspondingly (p<0.01). On 6-th month there was a statistically substantial difference in mean eGFR between subgroups of patients treated and not treated with febuxostat (p<0.05). Moreover, there was more pronounced decline in mean eGFR in patients with DN who received placebo, compared with subgroup without DN taking placebo (p<0.01). Conclusions. The study demonstrated promising ability of febuxostat to prevent eGFR decline in patients with hyperuricemia with and without diabetic nephropathy associated with chronic kidney disease.

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Introduction.

Chronic kidney disease (CKD) is considered to be an irreversible pathologic process, and patients who have it are expected to experience a progressively worsening course [1]. The rate of disease progression varies with the cause, and various therapeutic interventions, such as control of hypertension and proteinuria, have been shown to decrease it [2]. Hyperuricemia has been associated with adverse outcomes in CKD. Increasing level of uric acid in blood may lead to acute kidney injury and hence at risk for development of CKD [3]. Moreover, hyperuricemia has been linked to macrovascular heart disease in diabetic CKD [4]. High uric acid levels have been reported to be associated with increased rates of decline in glomerular filtration rate (GFR) in cross-sectional studies [1,5]. Another well-known risk factor of CKD development is diabetic nephropathy (DN). Simultaneously, type 2 diabetes is the most common cause of CKD and end-stage renal disease worldwide [6]. In the United States 40% of the 29 million individuals with type 2 diabetes have diabetic kidney disease [7]. The classic description of DN involved progressive stages of glomerular hyperfiltration, microalbuminuria, overt proteinuria, and a decline in the GFR, eventually leading to dialysis [8,9]. Febuxostat is a xanthine oxidase inhibitor shown to be efficacious in hyperuricemia and gout [10,11]. It does not require dose modification in patients with kidney failure. Therapy with febuxostat has been shown to prevent renal damage in 5/6 nephrectomized rats [12]. One randomized controlled trial has demonstrated the efficacy of allopurinol in reducing the rate of decline in GFR in patients with CKD with estimated GFRs (eGFRs) < 60 mL/min/1.73 m2 [13]. It was confirmed that febuxostat is able to slow down CKD progression and reduce GFR decline in patients without DN [11]. However, the difference in febuxostat potential to prevent further GFR decline in patients with hyperuricemia, with and without DN associated with CKD was not comprehensively evaluated. In this context, we hypothesized that febuxostat might retard the progression of kidney disease in patients with hyperuricemia and CKD associated with DN.

Objectives.

To assess the efficiency of Febuxostat in preventing of further GFR decline in patients with hyperuricemia with and without diabetic nephropathy associated and chronic kidney disease.

Material and methods.

The prospective study enrolled 73 adult patients with hyperuricemia and CKD of 3A-4 stages (34 patients with DN and 39 without DN). The mean age was 62.4±10.3 years. In all cases, baseline and 6 months after beginning of the treatment uric acid serum levels, estimated glomerular filtration rate (eGFR) and urine protein creatinine index were calculated. In patients with DN mean eGFR was 39.68±8.86 ml/min/1.72 m^2, while in patients without DN it was 42.31±8.54 ml/min/1.72 m^2 (figure 1).

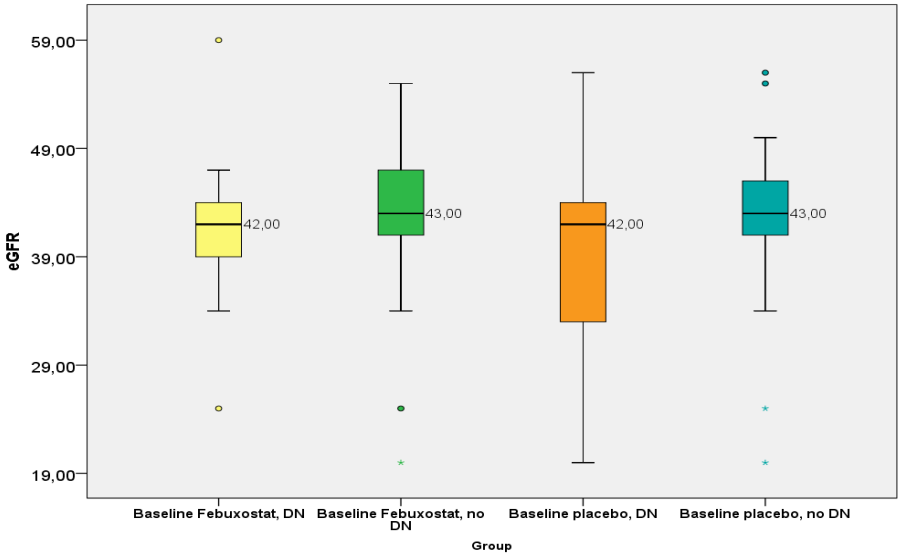

Figure 1. The box plot of the baseline eGFR (ml/min/1.72 m^2) in groups of patients. Notes: DN = diabetic nephropathy.

All patients with DN were randomized into two groups: treatment with febuxostat (Adenuric®) 40 mg daily (n=16) or placebo (n=18). Patients without DN were similarly randomized: treatment with the same dose of febuxostat (n=20) or placebo (n=19). Statistical significance was considered when P value was <0.05.

Results.

In patients with DN who received febuxostat or placebo and in patients without DN who received febuxostat or placebo mean baseline eGFR showed no difference and was 40.31±9.62, 39.11±8.37, 42.45±8.6, 42.16±8.7 accordingly (p>0.05). Six months after treatment with febuxostat, eGFR in patients with and without DN changed insignificantly and was 41.63±3.48 and 41.3±7.92 respectively (p>0.05). Conversely, in patients with and without DN, who received placebo, there was a significant decrease in mean eGFR six months after the treatment: 24.0± 6.51 and 33.26±4.78 correspondingly (p<0.01). On 6-th month there was a statistically substantial difference in mean eGFR between subgroups of patients treated and not treated with febuxostat (p<0.05). Moreover, there was more pronounced decline in mean eGFR in patients with DN who received placebo, compared with subgroup without DN taking placebo (p<0.01) table 1, figure 2.

Table 1. Detailed statistic characteristics of the eGFR (ml/min/1.72 m^2) dynamics in groups of patients

	N	Mean, ml/min/1.72 m^2	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Baseline Febuxostat, DN	16	40.31	9.62	2.41	35.18	45.44	15.0	59.0
On 6 MO Febuxostat, DN	16	39.81	2.07	0.52	38.71	40.92	34.0	43.0
Baseline Febuxostat, no DN	20	42.45	8.60	1.92	38.43	46.47	20.0	55.0
On 6 MO Febuxostat, no DN	20	41.30	7.92	1.77	37.59	45.01	20.0	54.0
Baseline placebo, DN	18	39.11	8.37	1.97	34.95	43.27	20.0	56.0
On 6 MO placebo, DN	18	31.61	3.29	0.78	29.97	33.25	25.0	38.0
Baseline placebo, no DN	19	42.16	8.70	2.00	37.96	46.35	20.0	56.0
On 6 MO placebo, no DN	19	38.74	5.43	1.25	36.12	41.36	32.0	45.0

Notes: DN = diabetic nephropathy, MO = month

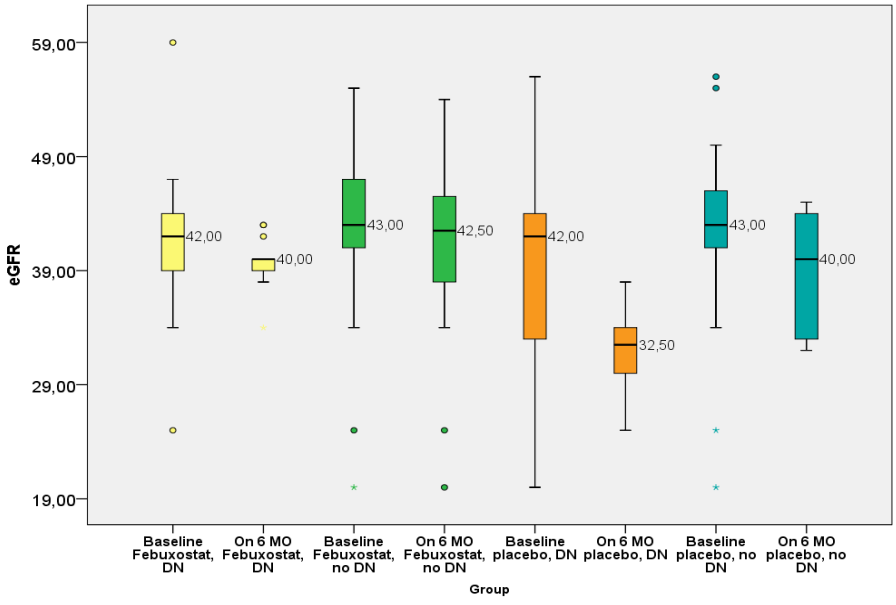

Figure 2. The box plot of the eGFR (ml/min/1.72 m^2) in groups of patients before and after treatment. Notes: DN = diabetic nephropathy, MO = month.

The dynamics of mean uric acid serum levels in all subgroups of patients demonstrated similar to eGFR tendency. However, there were no significant changes in urine protein creatinine index 6 months after the treatment compared to baseline in all subgroups. We observed no serious complications in subgroups treated with febuxostat.

Discussion.

There is a solid evidence that hyperuricemia is associated with adverse outcomes in CKD: increasing level of uric acid in blood may lead to acute kidney injury and to development of CKD [3]. Another well-known risk factor of CKD development is diabetic nephropathy [6]. Our study was dedicated to investigation of the efficiency of Febuxostat in preventing of further GFR decline in patients with hyperuricemia with and without diabetic nephropathy associated and chronic kidney disease. According to a literature analysis, there is a paucity of conflicting data dedicated to dedicated topic. In Sánchez-Lozada et al. work Febuxostat prevented renal injury in 5/6 nephrectomized rats with and without coexisting hyperuricemia. Because Febuxostat helped to preserve preglomerular vessel morphology, normal glomerular pressure was maintained even in the presence of systemic hypertension [12]. According to Kimura et al. data, among 443 patients who were randomly assigned, 219 and 222 assigned to febuxostat and placebo, respectively, were included in the analysis. There was no significant difference in mean eGFR slope between the febuxostat (0.23 ± 5.26 mL/min/1.73 m^2 per year) and placebo (−0.47 ± 4.48 mL/min/1.73 m^2 per year) groups (difference, 0.70; 95% CI, −0.21 to 1.62; P = 0.1). Subgroup analysis demonstrated a significant benefit from febuxostat in patients without proteinuria (P = 0.005) and for whom serum creatinine concentration was lower than the median (P = 0.009). The incidence of gouty arthritis was significantly lower (P = 0.007) in the febuxostat group (0.91%) than in the placebo group (5.86%). Adverse events specific to febuxostat were not observed [11]. Conversely, in another study 45 patients in the febuxostat group and 48 in the placebo group were analyzed. Mean eGFR in the febuxostat group showed a nonsignificant increase from 31.5±13.6 (SD) to 34.7±18.1mL/min/1.73 m^2 at 6 months. With placebo, mean eGFR decreased from a baseline of 32.6±11.6 to 28.2±11.5mL/min/1.73 m^2 (P=0.003). The difference between groups was 6.5 (95% CI, 0.08-12.81) mL/min/1.73 m^2 at 6 months (P=0.05). 17 of 45 (38%) participants in the febuxostat group had a >10% decline in eGFR over baseline compared with 26 of 48 (54%) from the placebo group (P<0.004), febuxostat slowed the decline in eGFR in CKD stages 3 and 4 compared to placebo [14]. There is another ongoing trial dedicated to this topic [15]. In our study application of febuxostat on dose 40 mg daily in patients with hyperuricemia and CKD of 3A-4 stages associated with DN allowed to prevent further eGFR decline. However, we observed no such effect in patients without DN, we explain such phenomena by relatively small number of cases and it was a main limitation of our study. Moreover, in multicenter open-label study of long-term administration of febuxostat in patients with hyperuricemia including gout demonstrated no noteworthy adverse events or adverse drug reactions in the patients with renal dysfunction, and no differences in drug efficacy up to 60 mg/d were noted between the patients with moderate or mild renal dysfunction and those with normal renal function [16]. In our study application of febuxostat also demonstrated excellent safety profile: there were no serious complications in all groups of patients.

Conclusions.

The study demonstrated promising ability of febuxostat (Adenuric®) to prevent eGFR decline in patients with hyperuricemia with and without diabetic nephropathy associated with chronic kidney disease. There was no difference in eGFR 6 months after treatment with febuxostat in patients with and without DN, which enlights its renoprotective equivalence in both subgroups. Treatment with febuxostat demonstrated no serious complications. However, there is an urge in further confirmation of such results in larger long-term studies.

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