https://doi.org/10.34883/PI.2022.14.3.002
UDC 616.72-002.78-06:616.12-008.331.1-02:616.61]-085.272

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Efficiency of Febuxostat in Gout Patients with Arterial Hypertension and Reduced Glomerular Filtration Rate: An Exploratory Study

Conflict of interest: nothing to declare.
Authors' contribution: Dubkova A. – analysis of literary sources; Tsymbalyuk T. – observation of patients; Krylova A. – concept and design of the study, analysis of the obtained data; Bortkevich O. – formulation of conclusions; Giresh I. – design of the text of the work; Bohdan M. – preparation the text of the work.
The article is published in the author's edition.

Submitted: 15.02.2022
Accepted: 26.05.2022
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Abstract

Purpose. To evaluate the efficacy and safety of febuxostat in gout patients with arterial hypertension and reduced glomerular filtration rate.
Materials and methods. The current prospective study included 36 patients with gout for an average of 5.5 (IQR 3.25–10.00) years. Depending on the clinical manifestations of gout, patients are divided into patients with tophi (16 people) and without tophi (20 people). Among the included patients were 12 women and 24 men with a mean age of 60.00 (IQR 45.25–65.75) years. Before treatment, the level of systolic blood pressure was 160.00 (IQR: 150.00–170.00) mmHg, diastolic – 92.00 (IQR: 90.00–100.00) mmHg, the level of GFR was 64.14 (IQR 51.57–88.36) ml/min/1.73 m^2. For the treatment were used febuxostat at a dose of 80 mg 1 time per day for 1 month.
Results. The average level of uric acid before therapy was 535.50 (IQR 496.50–625.75) μmol/l, two weeks later – 495.50 (IQR 442.50–534.00) μmol/l, a month later – 379.00 (IQR 366.50–403.25) μmol/l. The creatinine level decreased from 101.00 (IQR 78.00–121.00) μmol/l to 96 (IQR 76–120) μmol/l after a month. Statically significant ($p<0.05$) increased GFR from 64.14 (IQR 51.57–88.36) ml/min/1.73 m^2 before treatment to 68.61 (IQR 51.72–91.1) ml/min/1.73 m^2 after. Significant decrease arterial hypertension was obtained after 1 month of febuxostat use (systolic blood pressure – 150.00 (IQR: 136.00–160.00) mm Hg ($p<0.001$), diastolic – 90.00 (IQR: 80.00–94.00) mm Hg ($p<0.001$)) without changing antihypertensive therapy. There was a tendency to reduce the level of total cholesterol, which was – 6.15 (IQR 5.25–6.7) mmol/l before treatment, 5.7 (IQR 5.2–6.4) mmol/l after a month, but statistically insignificant ($p<0.06$).
Conclusion. The use of febuxostat in patients with arterial hypertension and reduced glomerular filtration rate can effectively reduce blood pressure and improve renal function.
Keywords: gout, uric acid, arterial hypertension, glomerular filtration rate, febuxostat

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Эффективность применения фебуксостата у пациентов с подагрой в сочетании с артериальной гипертензией и сниженной скоростью клубочковой фильтрации: предварительные результаты

Конфликт интересов: не заявлен.
Вклад авторов: Дубкова А.Г. – анализ литературных источников; Цымбалюк Т.С. – наблюдение за пациентами; Крылова А.С. – концепция и дизайн исследования, анализ полученных данных; Борткевич О.П. – формулировка выводов; Гиреш И.И. – оформление текста работы; Богдан М.В. – подготовка текста работы.
Статья опубликована в авторской редакции.

Подана: 15.02.2022
Принята: 26.05.2022
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Резюме

Цель. Оценка эффективности и безопасности применения препарата фебуксостат у пациентов с подагрой в сочетании с артериальной гипертерзией и сниженной скоростью клубочковой фильтрации.
Материалы и методы. В текущее проспективное исследование включено 36 пациентов, страдавших подагрой в среднем 5,5 года (IQR 3,25–10,00). В зависимости от клинических проявлений подагры пациенты разделены на пациентов с тофусной (16 человек) и бестофусной (20 человек) формами. Среди включенных пациентов было 12 женщин и 24 мужчины со средним возрастом 60,00 (IQR 45,25–65,75) года. До лечения уровень систолического АД составил 160,00 (IQR: 150,00–170,00) мм рт. ст., диастолического – 92,00 (IQR: 90,00–100,00) мм рт. ст., уровень СКФ составил 64,14 (IQR 51,57–88,36) мл/мин/1,73 м^2. Для лечения фебуксостат использовали в дозе 80 мг 1 раз в сутки в течение 1 месяца.
Результаты. Средний уровень мочевой кислоты до начала проведения терапии составлял 535,50 (IQR 496,50–625,75) мкмоль/л, через две недели – 495,50 (IQR 442,50–534,00) мкмоль/л, через месяц – 379,00 (IQR 366,50–403,25) мкмоль/л. Уровень креатинина снизился с 101,00 (IQR 78,00–121,00) мкмоль/л до 96 (IQR 76–120) мкмоль/л через месяц. Статически достоверно ($p<0,05$) повысилась СКФ от 64,14 (IQR 51,57–88,36) мл/мин/1,73 м^2 до лечения до 68,61 (IQR 51,72–91,1) мл/мин/1,73 м^2. Статистически достоверное снижение АД получено через 1 месяц применения препарата (систолическое АД – 150,00 (IQR: 136,00–160,00) мм рт. ст. ($p<0,001$), диастолическое – 90,00 (IQR: 80,00–94,00) мм рт. ст. ($p<0,001$)) без изменения антигипертензивной терапии. Наблюдалась тенденция к снижению показателей общего холестерина, который составлял 6,15 (IQR 5,25–6,7) ммоль/л до начала лечения, 5,7 (IQR 5,2–6,4) ммоль/л через месяц, однако данные статистически недостоверны ($p<0,06$).
Заключение. Применение фебуксостата у пациентов с артериальной гипертензией и сниженной скоростью клубочковой фильтрации позволяет эффективно снизить уровень АД и улучшить показатели функции почек.
Ключевые слова: подагра, мочевая кислота, артериальная гипертензия, скорость клубочковой фильтрации, фебуксостат

■ INTRODUCTION

Hyperuricemia is a disorder of metabolism of uric acid (UA) with an increase of its level in blood cerum above 360 μmol/l in men and 320 μmol/l in women [1]. As a clinical feature among patients hyperuricemia is a risk factor for cardiovascular death, metabolic syndrome, hypertension and nephrolithiasis [2] and in patients with hypertensive disease displays the renal hemodynamic disorder and can cause microalbuminuria and endothelial dysfunction [3]. Hyperuricemia induces the development of hypertension in two stages: in the early stage hyperuricemia activates the renin-angiotensin-aldosterone system, reduces nitric oxide (NO) levels that leads to vasoconstriction, which is reversible if an urate-lowering therapy is used. In the second stage, the entry of uric acid into vascular smooth muscle cells (VSMCs) causes the proliferation of these cells, the development of secondary arteriosclerosis and natriuresis disorders that leads to salt-sensitive hypertension development, which can be incurable with urate lowering therapy (ULT) [4]. Uric acid has a direct immunomodulatory effect, which has an impact on the inflammatory cascade associated with arteriosclerosis, and consequently with cardiovascular diseases (CVD). Nonspecific inflammation plays a central role in coronary heart disease developing, additionally, it was estimated that elevated levels of CRP and IL-6 are associated with an increased risk of CVD. It is known that monosodium urate (MSU) crystals activate NLRP3 inflammasomes, that leads to the formation of high levels of IL-1β and IL-18, which is an indication of acute gout attacks. It is interesting to mention that cholesterol activates the same type of inflammasomes before atherosclerotic lesions formation [5–7].

A study that compares febuxostat and allopurinol in a cohort of 141 outpatients who underwent cardiac surgery with UA levels >475.9 μmol/l (8 mg/dL) and who did not undergo urate lowering therapy (ULT), has estimated that febuxostat has an antihypertensive impact on the 6th month, which is not observed among patients' group, who was given allopurinol, the severeness of uricemia and oxidative stress has decreased less successfully compared to the patients in the febuxostat group [8, 9].

In the Zhang study of 2020, patients were given the drug febuxostat per os at a dose of 40 mg in combination of atorvastatin at a dose of 40 mg for 90 days of treatment, levels of TNF-α, IL-1β and serum CRP, as well as uric acid levels was reduced significantly ($p<0.05$). The size of plaques in carotid artery decreased significantly after the treatment in both groups ($P<0.05$). The authors made a conclusion that combination of febuxostat with atorvastatin allows to reduce the serum uric acid level and the level of proinflammatory cytokines. Also it allows to reduce the grows of carotid plaques [10]. Patients with third and fourth stage of chronic kidney disease had a higher glomerular filtration rate (GFR) in the febuxostat group compared with the placebo group [11, 12]. Statistically significantly lower level of blood creatinine was obtained in the febuxostat group with a duration of treatment of more than 6 months [13, 14].

■ PURPOSE OF THE STUDY

To evaluate the efficacy and safety of febuxostat in gout patients with arterial hypertension and reduced glomerular filtration rate.

■ MATERIALS AND METHODS

The current study was done at the Kyiv City Clinical Hospital № 7, according to the aim of the study, there were included 36 patients (12 women and 24 men) aged 42 to 65

patients with gout. All participants have agreed to participate in the study. The diagnosis of gout was established on the basis of the ACR / EULAR criteria of 2015 [15]. The general characteristics of the examined patients are presented in a Table 1.

As it is seen in the Table, the average age of patients was 60 years (IQR 45.25–65.75). The average duration of the disease was 5.5 years (IQR 3.25–10.00). Depending on the clinical manifestations of gout, patients are divided into two groups with tophi (16 people) and without tophi (20 people). For the treatment were used febuxostat at a dose of 80 mg 1 time per day for 1 month.

Methods of the study

1. General clinic: Collection of Complaints and Anamnesis, Objective Examination, questionnaires (Filling in Patient-Adapted Questionnaires, visual analogue scale, VAS).
2. Laboratory: Uric acid, CRP, ESR, Creatinine, Cholesterol, Bilirubin, ALT, AST.
3. Gout activity was determined by the gout activity score (gas) [16], which was calculated by the formula: gas = 0.09 × number of attacks during last 12 months + 1.01 × √UA + 0.34 × VAS patient's pain + 0, 53 × ln (1 + number of tofi), where UA is uric acid (mg/dL), VAS is a visual analogue scale of pain (cm).
4. The degree of glomerular filtration rate was determined with the use of the formula MDRD [17].
5. Methods of biomedical statistics. For statistical data processing there were used a software and mathematical complex of a personal computer Microsoft Excel 2007 (Microsoft) and computer programs for statistical analysis and data processing Biostatistics, STATISTICA® 6.0 (StatSoftInc., USA), SPSS Statistics 20 (IBM, USA).

■ RESULTS

During the analysis of the intensity of pain with the scale of VAS, there was found a statistically significant ($p<0.05$) reduction of parameters (Table 2) after the treatment. A decrease of gout activity was also indicated due to the febuxostat intake ($p<0.02$), which was confirmed with a decreased level of inflammation, such as CRP and ESR (Table 2).

Table 1
Characteristics of the examined patients

Parameters	Values
Total quantity of the patients, Among them: Males Females	36 24 12
Average age, years	60.00 (IQR 45.25–65.75)
Duration of the illness, years	5.50 (IQR 3.25–10.00)
Tophi form Form without tophi	16 20
The number of joints involved during attacks	5.5 (IQR 4.00–6.00)
Number of attacks during last year	2.0 (IQR 1.0–3.00)
Number of patients who have comorbidities: hypertension coronary heart disease diabetes mellitus, type II	 18 15 8

As a result of the study, there was estimated that the average level of uric acid among patients before treatment was – 535.50 (IQR 496.50–625.75) μmol/l, two weeks later – 495.50 (IQR 442.50–534.00) μmol/l, in a month – 379.00 (IQR 366.50–403.25) μmol/l. There were detected changes in creatinine levels, which were before treatment 101.00 (IQR 78.00–121.00) μmol/l, a month later – 96 (IQR 76–120) μmol/l. Accordingly, GFR values have changed from 64.14 (IQR 51.57–88.36) ml/min/1.73 m^2 before treatment, to 68.61 (IQR 51.72–91.1) ml/min/ 1,73 m^2 one month after treatment. Additionally, there was a tendency of reduction of the level of total cholesterol during the treatment, which was – 6.15 (IQR 5.25–6.7) mmol/l before treatment, 5.7 (IQR 5.2–6.4) mmol/l in 1 month (Table 3).

No dynamics was indicated in laboratory parameters of bilirubin, liver markers, which in most patients were within normal limits before inclusion to the study.

There was observed the dynamics of blood pressure: before taking febuxostat, the level of systolic blood pressure was 160.00 (IQR: 150.00–170.00), diastolic – 92.00 (IQR: 90.00–100.00) mm Hg. Art. Statistically significant decrease in indicators was obtained after 1 month of drug use (systolic blood pressure – 150.00 (IQR: 136.00–160.00) mm Hg ($p<0.001$), diastolic – 90.00 (IQR: 80.00–94.00) mm Hg ($p<0.001$)) without changing antihypertensive therapy (Table 4).

■ DISCUSSION

Despite the fact of existence of advances in the treatment of gout arthropathy during recent decades, gout remains an urgent problem today. The patients with several comorbidities are detected increasingly, such as with high blood pressure or kidney disease. Application of urate-lowering therapy can effectively adjust the level of uric

Table 2
Dynamics of gout arthropathy activity before and after febuxostat treatment

Parameter	Before treatment		After 1 month of treatment		P
	Me	IQR	Me	IQR	
VAS, mm (0–100)	42	40–49.5	35	32–42	0.05
gas	5.15	4.85–5.94	5.10	4.81–5.40	0.02
CRP, mg/L	13.22	9.28–16.55	6.05	4.35–7.30	0.001
ESR, mm/hr	19.00	17.25–28.50	13.50	10.25–15.75	0.001

Note: * Wilcoxon test was used, the reliability of the differences $p<0.05$.

Table 3
Dynamics of general clinical parameters before and after treatment with febuxostat

Parameter	Before treatment		After 1 month of treatment		P
	Me	IQR	Me	IQR	
Uric acid, μmol/l	535.50	496.50–625.75	379.00	366.50–403.25	0.001
GFR, ml/min/ 1.73 m^2	64.14	51.57–88.36	68.61	51.72–91.1	0.05
Creatinine, μmol/l	101.00	78.00–121.00	96	76–120	0.02
Total cholesterol, mmol/l	6.15	5.25–6.7	5.7	5.2–6.4	0.06

Note: * Wilcoxon test was used, the reliability of the differences $p<0.05$.

Table 4
Dynamics of general clinical parameters before and after treatment with febuxostat

Parameter	Before treatment		After 1 month of treatment		P
	Me	IQR	Me	IQR	
SBP, mm Hg	160	150–170	150	136–160	0.001
DBP, mm Hg	92	90–100	90	80–94	0.001

Note: * Wilcoxon test was used, the reliability of the differences p<0.05.

acid, but the effect of this group of drugs in patients with comorbidities is still poorly understood. In 2019 a study was conducted among patients with hyperuricemia (but not gout) and there were estimated cerebral, cardiovascular and renal events, as well as death from any cause during the therapy with febuxostat or without the usage of febuxostat [18]. As a result, patients who received febuxostat were 25 percent less likely to die or have a stroke, heart or kidney disease within three years than patients who did not.

In the current study, the intake of febuxostat allowed to achieve statistically significant reduction of pain severity according to VAS and reduction of gout activity (gas). In addition, the current study showed a significant effect of febuxostat on the purine metabolism among patients with hyperuricemia, statistically significant decrease of serum uric acid level, lower creatinine in the blood and increased GFR, which coincides with the results of previous studies [11–14]. These effects of febuxostat can be explained by the fact that it inhibits xanthine oxidase, which is known to be involved in various pathophysiological mechanisms of kidney damage, such as renal failure, renal fibrosis, accumulation of lipids and purines in the renal tubules [19].

Due to the fact that 87.5% of the examined patients suffered from hypertension, a statistically significant decrease in both systolic and diastolic blood pressure (without changes in antihypertensive therapy) was quite important, which may be associated with increased GFR, decreased level of uric acid in serum. Free radicals derived from uric acid can cause endothelial dysfunction and vasoconstriction by reducing NO availability and stimulating renin/angiotensin pathway activation and affecting vascular smooth muscle cells [20], and urate-lowering therapy reduce these effects.

Additionally, during the treatment was reduced a level of total cholesterol, although not statistically significant. There is evidence in the current literature of the effects of urate-lowering therapy on atherosclerosis, for instance, a study work of 2020 showed that a double dose of atorvastatin in combination with febuxostat can effectively reduce uric acid level, improve the "inflammatory profile" of patients and influence carotid plaques without increasing side effects [10]. It is known that uric acid crystals activate NLRP3 inflammasomes, leading to the formation of high levels of IL-1β and IL-18, which is characteristically to acute attacks of gout, and cholesterol activates the same inflammasome before occurrence of atherosclerotic lesions [5–7].

In addition, hyperuricemia correlates with number of inflammatory parameters levels, such as white blood cell quantity, CRP, ESR, IL-6, IL-1, IL-18 and TNF [7, 10, 21], which are involved in the development of acute gout arthritis. In the current study, it was found a statistically significant reduction of levels of inflammatory parameters such as CRP and ESR.

In the current study there were no data about the dynamics of laboratory parameters of bilirubin, liver markers, which were indicated in the numbers within normal values before inclusion to the study among most of the patients, and therefore no side effects were observed.

Further research is necessary to confirm these data in a larger sample of patients.

■ CONCLUSION

The use of febuxostat in patients with arterial hypertension and reduced glomerular filtration rate can effectively reduce blood pressure and improve renal function.

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