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Is renoprotection real for patients with hyperuricemia?

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Number of patients with progressive chronic kidney disease (CKD) is increasing all over the world. One of the risk factors for CKD development and progression is increased serum uric acid (sUA) level. Possibly, control of hyperurcemia with urate lowering therapy drugs can slow the decline in kidney function.
***The objective*: to determine efficacy and safety of allopurinol and febuxostat in treatment of patients with CKD and hyperurcemia to reduce the sUA level and analyze its influence on glomerular filtration rate (GFR).**
***Materials and methods*. The study included 45 CKD patients (stages 3b-5) without other severe/decompensated diseases and contraindications to the allopurinol/febuxostat. All patients underwent a comprehensive clinical and laboratory examination, and were divided into the study groups: Group I (28 patients, 61.3±3.2 y.o., CKD3b-12, CKD4-10, on hemodialysis-6 patients) received febuxostat, Group II (24 patients, 60.7±4.1 y.o., CKD3b-9, CKD4-10, on hemodialysis – 5 patients) took allopurinol.**
***Results*. Achievement of the target level of sUA was significantly often registered in Group I: after 1 month – in 45.5% (in group II – in 15.9%, p<0.001); after 3 months – in 67.5% (in group II – 21.2% p<0.01); after 6 months, these figures were 90% and 37.1%, respectively (p<0.01). sUA level <300 μmol/l was accompanied by significant positive GFR changes in group I patients; in group II there was a gradual progression of GFR deterioration in 31.8% of patients.**
***Conclusions*. In patients with pre-dialysis stages of CKD febuxostat demonstrates renoprotective abilities. Use of febuxostat in patients with CKD stage 3b-4 and in patients on hemodialysis is safe and more effective for target sUA level achievement than the use of allopurinol.**
Keywords: *chronic kidney disease, hyperuricemia, febuxsostat, allopurinol, glomerular filtration rate, renoprotection.*

Чи реальна ренопротекція для пацієнтів із гіперурикемією?

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Кількість пацієнтів із прогресуючою хронічною хворобою нирок (ХХН) зростає щорічно в усьому світі. Одним із факторів ризику розвитку прогресування ХХН є підвищений рівень сечової кислоти (СК). Можливо, що досягнення контролю над гіперурикемією за допомогою препаратів уратзнижуючої дії може уповільнити прогресування втрати швидкості клубочкової фільтрації (ШКФ).
Мета дослідження: визначення ефективності і безпеки застосування фебуксостату та алопуринолу у пацієнтів із ХХН і гіперурикемією для зниження рівня СК та аналіз впливу такого лікування на ШКФ.
Матеріали та методи. Дослідження проведено за участю 45 пацієнтів із ХХН (стадії 3б-5) без наявних інших важких/декомпенсованих захворювань та протипоказань до застування алопуринолу/фебуксостату.
Усі пацієнти після повного клінічного і лабораторного обстеження були розподілені у групи. До I групи увійшли 28 пацієнтів віком 61,3±3,2 року (ХХН 3б стадії – 12 осіб, ХХН 4 стадії – 10, на лікуванні гемодіалізом – 6 пацієнтів), які одержували фебуксостат. До II групи включено 24 пацієнти віком 60,7±4,1 року (ХХН 3б стадії – 9 осіб, ХХН 4 стадії – 10, на гемодіалізі – 5 пацієнтів), яким було призначено алопуринол.
Результати. Досягнення цільового рівня СК істотно частіше відбувалось у I групі: після 1 міс лікування у 45,5% пацієнтів (у II групі – у 15,9%; p<0,001); після 3 міс – у 67,5% (у II групі – у 21,2%; p<0,01); після 6 міс – у 90% пацієнтів I групи і у 37,1% пацієнтів II групи (p<0,01).
Досягнення стабільного рівня СК <300 мкмоль/л супроводжувалось істотними позитивними змінами ШКФ у пацієнтів I групи. Водночас у 31,8% пацієнтів II групи фіксували поступове зниження ШКФ.
Висновки. У пацієнтів з додіалізними стадіями ХХН фебуксостат продемонстрував ренопротективні властивості. Використання фебуксостату у пацієнтів із ХХН 3б-4 стадії та пацієнтів, які лікуються гемодіалізом, є безпечним та більш ефективним для досягнення цільових рівнів СК, ніж використання алопуринолу.
Ключові слова: *хронічна хвороба нирок, гіперурикемія, фебукстотат, алопуринол, швидкість клубочкової фільтрації, ренопротекція.*

Реальна ли ренопротекция для пациентов с гиперурикемией?

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Количество пациентов с прогрессирующей хронической болезнью почек (ХБП) растет ежегодно во всем мире. Одним из факторов риска развития прогрессирования ХБП является повышенный уровень мочевой кислоты (МК). Возможно, что достижение контроля над гиперурикемией с помощью препаратов снижающего действия может замедлить прогрессирование потери скорости клубочковой фильтрации (СКФ).

Цель исследования: определение эффективности и безопасности применения фебуксостата и аллопуринола у пациентов с ХБП и гиперурикемией для снижения уровня МК и анализ влияния такого лечения на СКФ.

Материалы и методы. Исследование проведено с участием 45 пациентов с ХБП (стадии 3б-5) без других тяжелых/декомпенсированных заболеваний и противопоказаний к применению аллопуринола/фебуксостата.

Все пациенты после полного клинического и лабораторного обследования были распределены в группы. В I группу вошли 28 пациентов в возрасте 61,3±3,2 года (ХБП 3б стадии – 12 человек, ХБП 4 стадии – 10, на лечении гемодиализом – 6 пациентов), получавших фебуксостат. Во II группу включены 24 пациента в возрасте 60,7±4,1 года (ХБП 3б стадии – 9 человек, ХБП 4 стадии – 10, на гемодиализе – 5 пациентов), которым было назначено применение аллопуринола.

Результаты. Достижение целевого уровня МК существенно чаще происходило в I группе: после 1 мес лечения у 45,5% пациентов (во II группе – у 15,9%; $p<0,001$); после 3 мес – у 67,5% (во II группе – у 21,2%; $p<0,01$); после 6 мес – у 90% пациентов I группы и у 37,1% пациентов II группы ($p<0,01$).

Достижение стабильного уровня МК <300 мкмоль/л сопровождалось существенными положительными изменениями СКФ у пациентов I группы. В то же время у 31,8% пациентов II группы фиксировали постепенное снижение СКФ.

Выводы. У пациентов с додиализными стадиями ХБП фебуксостат продемонстрировал ренопротективные свойства. Использование фебуксостата у пациентов с ХБП 3б-4 стадии и пациентов, лечащихся гемодиализом, является безопасным и более эффективным для достижения целевых уровней МК, чем использование аллопуринола.

Ключевые слова: *хроническая болезнь почек, гиперурикемия, фебукстотат, аллопуринол, скорость клубочковой фильтрации, ренопротекция.*

Over the last few decades, there has been a significant increase in chronic kidney disease (CKD) incidence around the world. Thus, according to the CDC USA, the frequency of this pathology is becoming epidemic and the prevalence of CKD stage 3 reaches 11.5% [1]. At this stage of the pathological process, CKD is a progressive and irreversible condition that significantly reduces the quality of life and life expectancy, requires significant medical and social investments in treatment and care of such patients.

Taking into account the lack of effective pharmacologic treatment for CKD and the long asymptomatic course of this pathology and therefore the «escape» of such patients from the attention of health professionals at early stages of disease, there is an urgent need in identification of the risk factors for increasing prevalence of CKD in different populations to determine the most effective approaches to prevention of renal damage and development of renoprotective drugs. One of the intensively investigated factor which have systemic negative impact on metabolic processes, cardiovascular disease morbidity and mortality and directly connected with renal function is hyperuricemia (HU) [2–9].

At present the number of current epidemiological studies indicate a significant effect of serum uric acid (sUA) on the development and progression of CKD. According to the study of R.P. Obermayr et al. (2008) [10], where the data from 21,475 healthy individuals was analyzed, even a slightly elevated sUA level (> 7.0 mg/dL (> 416 μmol/l) was associated with a doubling of the risk of developing CKD. In a study of 13,338 participants with preserved renal function – the risk of CKD increases 1.1-fold for every 1.0 mg/dL (59.5 μmol/l) increase of sUA concetration after age and other metabolic parameters adjustment [11].

The negative influence of HU on renal condition and function today is explained by a number of pathogenetic mechanisms that continue to be studied. Among them are: the development of HU-related hyperuricosuria and hyperglycemia with formation of UA crystals deposits in nephron collecting tubules in lower urine pH, which promotes further crystal formation and adhesion to the tubular epithelium; initiation of chronic inflammatory reaction in focuses of crystal deposition, including kidneys [8–12]. Non-crystallization effects of HU were demonstrated in experimental animals: even a mild increase in sUA led to the systemic elevation of blood pressure and glomerular hypertension in rats due to the development of systemic endothelial dysfunction [13].

The same mechanism of action of HU is indicated by other experimental data. In vitro it has been shown that HU reduces the synthesis of NO, thereby contributing to the development of the local endothelial dysfunction; in experiment also have been confirmed that HU caused arteriolopathy of the afferent arteries of the glomeruli and trigger the development of tubulo-interstitial fibrosis by activating RAAS; it is also shown that UA activates cytoplasmic phospholipase A2 and inflammatory transcription of NF-κB, which leads to inhibition of proliferation in proximal tubules.

Other identified effects of HU include a systemic increase in the synthesis of proinflammatory cytokines (including tumor necrosis factor alpha) and a local increase in chemokine expression (including MCF-1, monocyte chemotaxis factor) in the kidneys and COX-2 in blood vessels. Reduction of the sUA level reduces tubulo-interstitial sclerosis – both in the nephrectomy model and in diabetic nephropathy [7, 11, 14].

According to the results of the retrospective cohort study of healthy men aged 20–60 years, conducted in Japan using the annual survey and laboratory monitoring of the employees of several big companies in the period 2009–2014 (12,413 people) found the prevalence of HU in this cohort 21%, demonstrated and confirmed important significant relationships of sUA with other metabolic processes. Thus, significantly higher levels of glycated hemo-

globin and lower levels of high-density lipoprotein cholesterol (HDL cholesterol) were found in men with HU.

Analysis of data included in the study for 5 years of observation showed that the development of HU contributed to a decrease in GFR, and a decrease in the initially increased level of sUA – helped to slolw GFR loss: the difference for some subgroups in this study was up to 4.5 times [2]; the same study showed that the level of sUA was crucial for reducing GFR during 5 years of follow-up.

At the same time, current studies of allopurinol use in treatment of CKD patients failed to demonstrated it efficacy for slowing the CKD progression [14]. Given the significant increase in the number of adverse events with the use of therapeutic doses of allopurinol on the background of initially reduced GFR (including severe) and existing recommendations to reduce the dose in the presence of CKD, which in most cases does not achieve target levels in patients with GFR < 60 ml/min, the study of probable renoprotective effect of non-purine selective inhibitor of xanthine oxidase – febuxostat attracts a lot of attention from researchers around the world.

Thus, a meta-analysis of the observational and controlled trials [15, 16] showed that the use of febuxostat in patients with CKD and HU reduced serum creatinine slightly; moreover, in patients with CKD and HU with GFR of 15–60 ml/min/1.73 m^2, it was found that the use of febuxostat reduced the rate of progression of GFR loss. Other authors indicate that in such patients febuxostat effectively reduces the level of sUA and has a positive effect on GFR, albuminuria and blood pressure [17–20].

Nevertheless there are no recommendations about febuxostat use for its renoprotective action in the published CKD international guidelines, because of declared lack of scientific data about the subject [21–25].

At present time also the target levels of sUA are set only for patients with HU and gout, while the optimal values of UA in serum for prevention / inhibition of CKD progression (GFR loss) – remain unclear.

The objective: to determine the efficacy and safety of allopurinol and febuxostat in treatment of patients with CKD to reduce the level of sUA and to analyze the effect of such treatment on glomerular filtration rate (GFR).

MATERIALS AND METHODS

The study was conducted in 2020–2021 at the Department of Family Medicine, Department of Nephrology and Renal Replacement Therapy (National Healthcare University of Ukraine, Kyiv, Ukraine) based on KNP KOR «Kyiv Regional Clinical Hospital», Department of Traumatology and Orthopedics of Bogomolets National Medical University; Hemodialysis Center of the Brovarsky Multidisciplinary Clinical Hospital; Clinic of Modern Rheumatology (Kyiv, Ukraine); Department of Internal Diseases #2 (I. Horbachevsky Ternopil Medical University, Ternopil, Ukraine). The study included 45 patients with HU (serum UA >416 μmol/l) and CKD (stages 3b-5). All patients consented to participate in the study.

Patients with recent acute kidney injury, acute renal failure, acute glomerulonephritis, advanced heart failure, with kidney transplant, systemic connective tissue diseases, infections, cancer, other severe/decompensated diseases, Hb <80 g/l; ALT and/or AST >3 times exceed the normal limit; and other conditions that could affect the parameters studied and the patient's life expectancy; contraindications to the use of allopurinol/febuxostat – were not included. At the time of enrollment in the study, patients were either not taking ULT or had completed a 2-week withdrawal period (10 patients). The target level of UA for patients with pre-dialysis stages of CKD was set at 300 μmol/l, for patients on hemodialysis - was not set.

All patients underwent a comprehensive clinical and laboratory examination, which included medical history, complete physical and joint examination, laboratory tests (full blood count, creatinine, UA, ALT, AST, blood glucose, HbA1c), GFR calculation (CKD-EPI).

Further the patients were divided by their consent into one of the study groups for the treatment of HU:

- group I received febuxostat (Liquestia, 40–120 mg/day),
- group II – allopurinol (50–300 mg/day – for patients with pre-dialysis CKD stages and up to 800 mg/day – for patients on hemodialysis).

Clinical and laboratory examination was repeated after 2 weeks, 3 months and 6 months of treatment; sUA levels were determined with individual frequency, depending on the dynamics of the indicator. Doses of ULT drugs were corrected depending on the dynamics of sUA, taking into account GFR (for allopurinol).

Statistic analysis was performed with program Statistica 10 with use of non-parametric methods and Mann-Witney U-test; the difference between parameters was considered significant in $p<0.05$.

The characteristics of the patients included in the study are presented in Table 1.

Table 1

Clinical and laboratory characteristics of the study patients

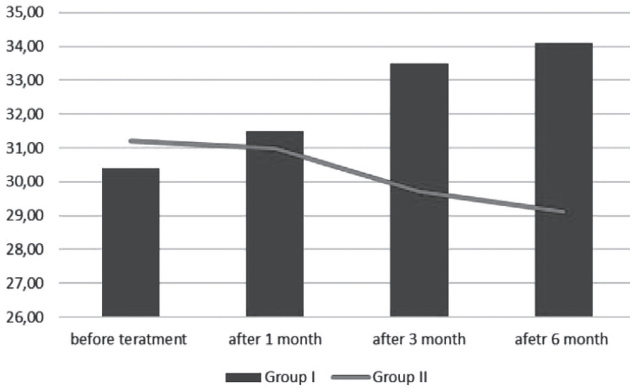
Parameter	Group I, n=28	Group II, n=24	p
Mean age, years	61,3±3,2	60,7±4,1	>0.05
Males, n (%)	17 (61,2)	14 (58,8)	>0.05
CKD 3b, n (%)	12 (43,2)	9 (37,8)	>0.05
CKD 4, n (%)	10 (35,7)	10 (41,7)	>0.05
Patients on hemodialysis, n (%)	6 (21,6)	5 (20,8)	>0.05
Comorbidities			
Gout, n (%)	16 (57,6)	13 (54,6)	>0.05
Chronic anemia, (Hb 81–119 g/l)	12 (42,9)	10 (41,7)	>0.05
NAFLD, n (%)	16 (57,6)	15 (62,5)	>0.05
AH, %	100	100	>0.05
DM, n (%)	10 (35,7)	7 (29,4)	>0.05
CVD, n (%)	15 (54,0)	13 (54,6)	>0.05
Urolithiasis, n (%)	4 (14,4)	4 (16,4)	>0.05
sUA, μmol/l	682,12±23,1	676,48±30,23	>0.05
GFR, ml/min	26,8±8,5	27,4±10,1	>0.05

Note: NAFLD – non-alcoholic fatty liver disease; AH – arterial hypertension; DM – diabetes mellitus; CVD – cardio-vascular disease.

Table 2

Dynamics of sUA level and GFR in patients of both groups with pre-dialysis stages of CKD

Group / timepoint	Group I, n=22		Group II, n=19	
	sUA, μmol/l	GFR, ml/min	sUA, μmol/l	GFR, ml/min
Baseline	553,1±15,8	30,4±2,2	539,8±19,3	31,2±2,6
In 1 month	429,7±25,1*	31,5±2,7	466,5±29,3	31,0±2,7
In 3 months	372,8±13,6*	33,5±2,8*	433,5±36,7	29,7±2,4
In 6 months	302,5±11,5*	34,1±3,1*	447,2±25,1	29,1±3,0



Changes in GFR (ml/min) in patients with CKD stages 3–4 during study; Group I – treatment with febuxostat, Group II – treatment with allopurinol

As its shown in Table I all included patients had 3–5 comorbidities and took rather wide spectrum of concomitant medications for its treatment according to the national guidelines, the treatment remained stable during the study period.

RESULTS

All participants showed a significant decrease in the level of sUA under the influence of ULT drugs, however, the achievement of the target level of UA was significantly more often registered in Group I. The dynamics of the indicators in patients with pre-dialysis CKD stages is shown in Table 2.

Analysis of the dynamics of sUA decrease in the studied groups showed that after 1 month of treatment 10 patients reached the target level of sUA in group I (45.5%) and 3 patients in group II (15.9%), $p<0.001$; after 3 months of treatment in group I 67.5% reached the target level of sUA, and in group II – 21.2% ($p<0.01$); after 6 months, these figures were 90% and 37.1%, respectively ($p<0.01$), while it should be noted that in group II, all patients who reached the sUA level about 300 μmol/l were in CKD 3 subgroup.

We have not find any significant differences in sUA level achieved in 3 and 6 month of treatment in patients with different comorbidities.

At each study visit, the GFR (using the CKD-EPI formula) was re-determined in all patients, and as can be seen from the data presented in Table II, the achievement of sUA levels less than 300 μmol/L was accompanied by significant positive GFR dynamics in most patients (in 90% of patients, GFR increased compared with the baseline, on average – in group I – by 3.1±0.51 ml/min, while in group II there was a gradual progression of GFR deterioration – in 31.8% of patients, a downward trend – in other patients in the group. Starting from month 3 timepoint of the study GFR was significantly higher in patients of Group I, independently from comorbidities profile, comparing to patients from Group II ($p<0,05$).

An analysis of the dynamics of sUA levels in patients from the hemodialysis group showed the achievement of significantly lower level in patients treated with febuxostat comparing to the baseline and to the group treated with allopurinol.

During the study period, no serious adverse events (AE) were registered in study patients, mild and moderate adverse events (in total – 8 events) in the form of epigastric discomfort, transient increase in ALT/AST (up to 3 times from the upper limit of the laboratory normal level) and skin rashes were registered in 5 patients (2 patients took febuxostat and 3 – allopurinol).

Development of AEs did not lead to the discontinuation in study participation in any cases, but made impossible to increase the dose of allopurinol in 3 patients. It is worth to note that all cases of increase in ALT and / or AST level were determined in patients with comorbid non-alcoholic fatty liver disease.

Discussion. The problem of the increasing incidence of CKD in the world's population with the subsequent development of the end-stage renal disease requires clarification of not only the risk factors for this serious condition, but also the search for pharmacological drugs with renoprotective properties. Unfortunately, to date, the renoprotective activity of drugs with a previously proven positive effect on the kidney function (primarily – drugs that effect the RAAS system) is being questioned.

At the same time, the number of experimental and clinical studies are pointing on the negative impact of elevated serum uric acid levels on kidney function, development of metabolic disorders and comorbid diseases. Some researchers state that it is absolutely necessary to reduce the level of serum uric acid in order to prevent or slow down the progression of GFR loss in patients with CKD, prevention of CVD, metabolic syndrome and other pathological conditions, however, recommendations for the use of urate-lowering therapy for these purposes have not been approved. In our study, we compared the efficacy and safety of the use of classical ULT drugs – febuxostat and allopurinol for the treatment of HU in patients with CKD 3b-5 stage and analyzed the dynamics of GFR during 6 months of follow-up. It should be noted that the study was conducted in real practice, where all patients had 3–5 comorbid diseases and, in addition to HU and CKD, received a wide range of drug therapy for concomitant diseases, which could have influence on the study results.

Another limitation of the study is rather small number of cases analyzed and the relatively short follow-up period. An analysis of the results of the use of ULT in the above mentioned groups of patients showed that febuxostat is

more effective than allopurinol in achieving target levels of sUA in patients with pre-dialysis stages of CKD, with the same level of adverse events. The use of this ULT drug allowed a statistically significant improvement in GFR in this subgroup of patients, which suggests the presence of renoprotective properties in febuxostat, possibly associated not only with the achieved level of sUA, but also with the pleiotropic effects of this drug.

In hemodialysis patients, febuxostat was also more effective than allopurinol in achieving significantly lower sUA levels during the study period, the effect of which on patient health needs to be further investigated.

CONCLUSIONS

Use of febuxostat in patients with CKD stage 3b-4 and in patients on hemodialysis is more effective in reducing the level of sUA and achieving the target level of sUA than the use of allopurinol in the absence of serious adverse events within 6 months of therapy.

In patients with pre-dialysis stages of CKD, the use of febuxostat as part of treatment is accompanied by stabilization or statistically significant increase in GFR, which requires further studies to confirm the renoprotective properties of febuxostat and develop a standard treatment algorithm, possibly starting at earlier stages of CKD.

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