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The impact of urate-lowering therapy on kidney function (IMPULsKF)

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Abstract. *The concept of trial launched in Ukraine in 2017 with POEM design and 36-months duration is presented. It aims to investigate the impact of two target levels of urate-lowering therapy caused by hyperuricemia on kidney function and chronic kidney disease (CKD) progression measured by estimated glomerular filtration rate and albuminuria in 180 patients with gout (n = 90) and with CKD (n = 90). The main current tasks include: 1) evaluation of serum urate acid (SUA) level most potential preserving kidney function; 2) the new onset of gout attacks depending on SUA level, both in gout and CKD objects; 3) safety and side effects of target and ultra-low SUA levels for evidence-based urate-lowering therapy optimal regime in CKD and non-CKD with gout.*

Keywords: *urate-lowering therapy; kidney function; hyperuricemia; chronic kidney disease; gout*

Concept summary

This project aims to investigate the impact of two target levels urate-lowering therapy (ULT) caused by hyperuricemia (HU) on kidney function and CKD progression measured by eGFR and albuminuria (A).

This trial had been formulated by 2016 updated EULAR evidence-based recommendations for the management of gout as a perspective proposal task for future research [1].

The key points are: 1) an unknown target HU level and 2) the time duration of ULT resulting in preserved kidney function in two subject groups: a) with gout and b) without gout but highly elevated uricemia and CKD.

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In this study the optimal ULT for kidney function based on target SUA level in 36 months' treatment with either allopurinol or febuxostat will be determined.

The background and rationale

The extended 2016 EULAR updated report states that for patients on ULT, SUA level should be monitored and maintained to < 6 mg/dL (360 μmol/L). A lower SUA target (< 5 mg/dL; 300 μmol/L) to facilitate faster dissolution of crystals is recommended for patients with severe gout (tophi, chronic arthropathy, frequent attacks) until total crystal dissolution and resolution of gout. SUA level < 3 mg/dL (180 μmol/L) is not recommended in the long term [1].

Among EULAR proposals for future research is mentioned the optimal duration for prophylaxis of acute attacks when starting ULT, long-term impact of very low urate levels on the central nervous system, impact of ULT on kidney function.

Since 2013 we have been treating 2 groups of adults with gout and with CKD without gout to target SUA level less than < 5 mg/dL; 300 μmol/L. The preliminary results had been orally presented at 50th ERA-EDTA Congress (2015) showing that at least 4-year treatment with febuxostat improves GFR and BP control in patients with asymptomatic HU in non-diabetic CKD 2–3 [2]. Ultra-low SUA target was a benefit with more

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frequent side effects. Hence it could be part of renoprotection [3].

Taking into account the widespread of CKD, gout and availability of ULT it will be reasonable to ascertain the possibilities of allopurinol/febuxostat therapy in these patients. The research planed should be conducted to serve in primary care.

Methods

The main concept of this trial is POEM design (Patient Oriented Evidence that Matters) which addresses a widespread clinical problem to primary care physicians as well as nephrologists. This will encounter in their practice uses patient-oriented outcomes which have the potential to change our practice if the results are valid and applicable [4].

IMPULsKF is a Clinical Randomized Prospective Controlled Open Multicenter trial that randomly (by chance) assigns 180 participants in parallel groups. These patientswith high SUA level (> 8 mg/dL; 480 μmol/L) are going to be divided into 2 arms (90 + 90) 1) with gout (EULAR's criteria) and without gout but withpresence of CKD 1–4 stages.

There will be 2 target SUA levels in each group as 5 mg/dL (300 μmol/L) and ultra-low SUA < 3 mg/dL (180 μmol/L) achieved either with allopurinol or febuxostat. The data obtained will be compared with control group (45 with gout without CKD and 45 with CKD).

Ultra-low and normal UA level arms are provided concurrent enrolment and follow-up in this groups which will be selected by a random process. The basic study duration is going to befor 36months with additional 6 months recruitment period and 3 months post-trial analysis.

The data obtained will be analyzed by professional medical statisticians to present eGFR and A trends are based on the following: NNT depending target SUA levels, ARR, Likelihood ratio Positive Predictive Value, Odds Ratio and statistical differences between groups comparing Sensitivity and Specificity of both arms treatment.

Duration

36 months (plus 6 months before enrolment and 3 months post-trial analysis).

Primary and secondary outcomes

The primary outcome is comparison benefits of ULT to 2 different targets:

a) in Clinical reduction of new onset of acute gout attacks;

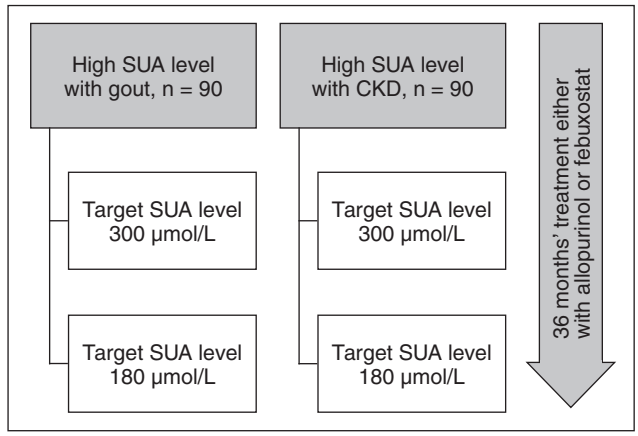
b) prevention of worsening of kidney function by eGFR measurement;

c) estimating CKD prognosis by eGFR and A level.

The secondary outcomes is comparison benefits of ULT to 2 different targets:

a) in cardiovascular risk diminution;

b) central and peripheral nervous system status;



Picture 1

c) comparison efficacy, side effects and cost utility between allopurinol and febuxostat;

d) impact of ACEI/ARB on SUA levels corrected by allopurinol/febuxostat in different CKD stages.

The current tasks also include:

1) to determine U-curve or directly proportional relationship between SUA and eGFR-EPI in CKD 1–4;

2) to evaluate the new onset of goat's acute attack which depends on SUA level and renal function.

Inclusion/exclusion criteria

Inclusion criteria: outpatient adult subjects with hyperurecemia (SUA level above 8 mg/dL (480 μmol/L)) either with gout or gout-free CKD 1–4 stages.

Exclusion criteria: CKD 5, severe forms of associated comorbidities and cardiovascular risk factors, including heart failure III-IV NYHA, stroke, peripheral arterial disease, obesity with BMI above 30 kg/m^2, hypertension 3 grade, insulin-dependent DM and any kind of cancer, inpatient intensive unit subjects.

Conflicts of interests. Author declares the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

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Вплив терапії, що знижує рівень сечової кислоти, на функцію нирок (IMPULsKF)

Резюме. Подано дані про дослідження, розпочате в Україні у 2017 році, із дизайном РОЕМ і тривалістю 36 місяців. Його метою є вивчення впливу двох цільових рівнів терапії, спрямованої на зниження підвищеного рівня сечової кислоти (гіперурикемія), на функцію нирок і прогресування хронічної хвороби нирок (ХХН), який визначали за розрахунковою швидкістю клубочкової фільтрації і рівнем альбумінурії, у 180 пацієнтів із подагрою (n = 90) і ХХН (n = 90). Основні поточні завдання включають: 1) оцінку рівня сечової кислоти в сироватці крові (СКСК), що має найбільший потенціал при збереженні функції нирок; 2) виявлення нових нападів подагри залежно від рівня СКСК у пацієнтів як із подагрою, так і з ХХН; 3) безпеку і побічні ефекти цільового і наднизького рівнів СКСК при оптимальному режимі доказової терапії, спрямованої на зниження рівня сечової кислоти, у осіб із ХХН і пацієнтів без неї, але з подагрою.

Ключові слова: терапія, спрямована на зниження рівня сечової кислоти; функція нирок; гіперурикемія; хронічна хвороба нирок; подагра

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Влияние терапии, снижающей уровень мочевой кислоты, на функцию почек (IMPULsKF)

Резюме. Представлены данные об исследовании, начатом в Украине в 2017 году, с дизайном РОЕМ и продолжительностью 36 месяцев. Его целью является изучение влияния двух целевых уровней терапии, направленной на снижение повышенного уровня мочевой кислоты (гиперурикемия), на функцию почек и прогрессирование хронической болезни почек (ХБП), которое определяли по расчетной скорости клубочковой фильтрации и уровню альбуминурии, у 180 пациентов с подагрой (n = 90) и ХБП (n = 90). Основные текущие задачи включают: 1) оценку уровня мочевой кислоты в сыворотке крови (МКСК), которая обладает наибольшим потенциалом при сохранении функции почек; 2) выявление новых приступов подагры в зависимости от уровня МКСК у пациентов как с подагрой, так и с ХБП; 3) безопасность и побочные эффекты целевого и сверхнизкого уровней МКСК при оптимальном режиме доказательной терапии, направленной на снижение уровня мочевой кислоты, у лиц с ХБП и пациентов без нее, но с подагрой.

Ключевые слова: терапия, направленная на снижение уровня мочевой кислоты; функция почек; гиперурикемия; хроническая болезнь почек; подагра