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The Current Access to Hypouricemic Therapy of Gout

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Abstract
Despite the availability of effective urate-lowering drugs, treatment of gout is often one of the most difficult problems to solve.
Purpose of the Study: To conduct a comparative analysis of hypouricemic drugs in patients with gout.

***Materials and* Methods**:The study included 60 patients with a definite diagnosis of gout who applied to the arthrological SCAL on the basis of the multidisciplinary clinic of the Tashkent Medical Academy for the purpose of therapy correction. Allopurinol was used as urate-lowering therapy at a starting dose of 100 mg/day, followed by an increase by 100 mg/day every 2-3 weeks until the target UA level was achieved. In cases of ineffectiveness of the maximum possible doses of allopurinol and/or the presence of adverse reactions associated with this drug, febuxostat was prescribed at an initial dose of 80 mg/day, which, if necessary, was increased to 120 mg/day. The Morisky-Green questionnaire was used to assess patients' adherence to therapy.

Results and Discussion: Adherence to regular drug therapy among patients with gout receiving allopurinol was 25% at a high level, 40% at an average level, and 35% at a low level. When using febuxostat, high adherence to therapy was detected in more than 50% of cases. Adherence to high-level lifestyle changes was 30%, medium 40%, low - 30%, and readiness to correct hypouricemic therapy was 38%, 45% and 17%, respectively, by level.
***Conclusions*:** Thus, compliance with recommendations for the management of patients with gout allows for high patient adherence to both drug treatment and lifestyle changes.

Keywords
Gout, Hyperuricemia, Allopurinol, Febuxostat, Adherence to Therapy

1. Introduction
Gout is a chronic disease associated with impaired uric acid metabolism, as a result of which the level of uric acid (UA) in the blood increases, crystals of the sodium salt of UA are deposited in the tissues, which is clinically manifested by recurrent acute arthritis and the formation of gouty nodes (tophi) [1 ,8]. According to population-based studies in the UK

and Germany, gout is the most common cause of inflammatory arthritis in men over 30 years of age, accounting for 1.4% of the total incidence [10, 12]. In the Russian Federation, 0.3% of the adult population suffers from gout [2].

Despite great advances in the diagnosis of gout, the availability of various guidelines for the management of such patients, its treatment remains sub-optimal, the proportion of patients receiving adequate ongoing therapy is low, which also contributes to an increase in the number of patients suffering from attacks of gouty arthritis and at risk of further damage to the joints and other life-threatening diseases complications.

The modern strategy for the treatment of gout is based on the recommendations of the Association of Rheumatologists of Russia (ARR, 2019) [1], the European League Against Rheumatism (EULAR, 2016–2018) [3,4], and the American College of Rheumatology (ACR, 2020) [11]. The latest recommendations for the management of patients with gout (May, 2020) are presented in the journal Arthritis Care & Research and include treatment of an acute attack of gout, indications for urate-lowering therapy, as well as recommendations for fluid and medications that are often prescribed to patients with comorbid conditions.

The general principles of therapy are that every patient with gout should be thoroughly informed about the pathophysiology of the disease, the availability of effective treatments, the principles of treatment of an acute attack of arthritis and the elimination of urate crystals by lifelong reduction of serum UA levels below the target level (360 μmol/l). Every gout patient should receive recommendations regarding lifestyle, including losing weight if necessary, stopping smoking, drinking alcohol (especially beer and hard liquor) and sweetened drinks, overeating, and excessive consumption of meat and seafood. Consumption of low-fat dairy products should be encouraged. Regular exercise should be recommended. Every patient with gout should be systematically screened to identify co-morbid conditions and cardiovascular risk factors, including chronic kidney disease (CKD), ischemic heart disease, heart failure, stroke, peripheral arterial atherosclerosis, obesity, hyperlipidemia, hypertension, 2 type of diabetes, the prevention and treatment of which should be considered an integral part of gout treatment [5, 7, 9].

Currently, international experts have identified indications for urate-lowering therapy (ULT) for asymptomatic HU, which are: persistent UA levels above 13 mg/dL (770 μmol/L) in men or 10 mg/dL (600 μmol/L) in women (these values increase the risk of nephrotoxicity, and UA may slow the progression of kidney disease and prevent these risks); renal excretion of ULT exceeding 1100 mg/day (this is associated with a 50% increase in the risk of developing ULT deposition in the form of stones, which is prevented by reducing its excretion by the kidneys to 800 mg/day) [3,4].

Assessing the adherence of gout patients to treatment in an outpatient setting has become relevant in recent years. US study showed that only 29% of patients with gout were taking urate-lowering therapy and only half of them achieved target serum UA levels [11]. According to authors from the UK, the frequency of prescription of urate-lowering drugs to patients with gout ranges from 32 to 38%, and only 39% of patients continue this therapy after the first year of observation [12]

One of the main reasons for the failure to achieve target levels of UA is the low compliance of patients with gout. A certain negative impact may also be caused by the lack of belief of both patients and many doctors that in most cases the goals of gout treatment can be fully achieved. Objective reasons include, unfortunately, frequent medical errors during urate-lowering therapy, which are either not prescribed or are carried out using an incorrect dose of drugs [7]. An increase in the frequency of exacerbations (regardless of the choice of xanthine oxidase inhibitor) when initiating therapy [6, 8], as well as the need for simultaneous administration of a large number of drugs (since 3/4 of patients with gout have at least one comorbidity) contribute to increased adherence to treatment

2. Materials and Methods

The study included 60 patients with a definite diagnosis of gout who applied to the arthrological SCAL on the basis of the multidisciplinary clinic of the Tashkent Medical Academy for the purpose of therapy correction. The diagnosis of gout was made based on the ACR/EULAR criteria (2015). Hyperuricemia was diagnosed according to the EULAR criteria (2006) with UA level >360 mmol/l.

Allopurinol was used as urate-lowering therapy at a starting dose of 100 mg/day, followed by an increase by 100 mg/day every 2–3 weeks until the target UA level was achieved. In cases of ineffectiveness (the target level of UA was not achieved) of the maximum possible doses of allopurinol and/or the presence of adverse reactions (ARs) associated with this drug (including according to medical history), febuxostat (Feblorica) was prescribed at an initial dose of 80 mg/day, which if necessary, increased to 120 mg/day.

To prevent attacks of acute arthritis, standard anti-inflammatory therapy was carried out with one of the NSAIDs in minimal therapeutic doses or colchicine 0.5 mg/day, and in case of intolerance or contraindications, GCs were prescribed at 7.5 mg/day in terms of prednisone. After 6 months, patients' adherence to urate-lowering therapy was determined using the Morisky-Green questionnaire, which included four questions. The patient had to independently answer the questions by choosing one of two answer options – “yes” or “no”, which were scored 0 or 1 point, respectively. Then the total score was calculated: 4 points – high adherence to therapy, 3 points – moderate, ≤2 points – low.

All patients underwent a complete clinical examination, including anthropometric measurements (body weight, height, body mass index), general clinical tests, lipid profile studies, glucose, uric acid, creatinine, urea, serum CRP,

ECG, echocardiography, ultrasound of the kidneys and joints , x-ray examination of joints. Additionally, levels of adherence to drug therapy and lifestyle modification in patients with gout were assessed.

3. Results and Discussion

Among the patients with gout examined, men accounted for 71%, women - 29%. The average age of the patients was 54.3±8.3 years, with the majority of patients aged 42 to 60 years. In most patients, the average duration of the disease was 4.57±1.35 years, that is, it did not exceed 5 years, the frequency of exacerbations of arthritis ranged from 1 to 4 attacks per year (average 2.23±0.32). Patients were predominantly affected by the first metatarsophalangeal joint (91%), ankle joints (62%), less frequently, involvement of the knee joints and small joints of the hands and elbow joints was noted (34%, 22%, 6%, respectively). Serium UA levels ranged from 392 to 775 mmol/l (mean 504.8±83.7 mmol/l).

Concomitant diseases were identified in 86% of patients, arterial hypertension predominated in 76% of patients. In 9 patients with gout, there was a history of poor tolerance to allopurinol: 4 had itchy skin, 2 had urticaria, and 3 had a more than twofold increase in ALT and AST levels. The opinion of the surveyed patients was collected regarding their awareness of compliance with hypouricemic dietary recommendations: 82% of patients did not follow the diet or systematically violated it. 64% of patients were not regularly seen by a doctor and did not receive therapy before inclusion in the study. Patients with gout in combination with arterial hypertension took antihypertensive drugs: ACE inhibitors (enalapril, perindopril, capoten) - 60% of patients, calcium antagonists (amlodipine) - 32% and β-blockers (metoprolol, bisoprolol) - 18% were used less frequently. 48% of patients with gout took low doses of thiazide diuretics, 70% took low doses of aspirin. After 6 months of follow-up, patients were asked to complete the Morisky-Green test to assess adherence to prescribed therapy. By the end of the observation (after 6 months), 68% of patients received urate-lowering therapy, 60% of them achieved the target sUA level, and in the group of patients taking febuxostat (Feblorica), this figure was higher and amounted to 76%. It should be noted that after 3 months of taking febuxostat (Feblorica), the target level of UA was achieved in 57% of patients, while at the same time, against the background of allopurinol, this figure was equal to 48%. Adherence to regular drug therapy among patients with gout receiving allopurinol was 25% at a high level, 40% at an average level, and 35% at a low level. When using febuxostat (Feblorica), high adherence to therapy was detected in more than 50% of cases. No independent refusal to take febuxostat (Feblorica) was registered. Adherence to high-level lifestyle changes was 30%, medium 40%, low - 30%, and readiness to correct hypouricemic therapy was 38%, 45% and 17%, respectively, by level.

4. Conclusions

Thus, adherence to recommendations for the management of patients with gout, which include constant use of urate-lowering drugs, adjustment of their dose until target values of uric acid in the blood serum are achieved, preventive anti-inflammatory therapy and regular monitoring of the patient's condition, allows achieving high patient adherence to both drug treatment and and lifestyle changes.

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