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EVALUATION OF 12-WEEK URATE-REDUCING THERAPY WITH ALLOPURINOL IN COMBINATION WITH THE NONSTEROIDAL ANTI-INFLAMMATORY DRUG MELOXICAM IN PATIENTS WITH GOUT

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ABSTRACT

Gout or gouty arthritis is a rheumatic disease of a systemic nature, the cause of which is an increased content of uric acid in the blood (more than 6.8 mg / dl). The condition of arthritis develops due to the crystallization of sodium monaurate in the synovial fluid, followed by phagocytosis and the formation of inflammasomes. It is the latter that are the main mechanism of systemic inflammation. Gout, what kind of disease it is and how to deal with it – you need to know, especially if a bone began to bother your leg. It appears in the area of the thumb joint. Among rheumatic pathologies, gout ranks second after osteoporosis. The disease occurs more often in men than in women. Hyperuricemia can be caused by excessive intake of purine bases into the body, the product of the decay of which it is. And they come mainly with food: red varieties of meat and fish, coffee, cocoa and chocolate, cheeses, sausages, smoked meats, alcoholic beverages. Incontinence in the use of these products inevitably leads to the deposition of urates in the tissues. In ancient times, not everyone could afford the abuse of such products, which is why gout was called the "disease of the aristocrats", because its presence indicated a certain level of well-being. The relationship between the development of gout, the severity of its signs and the volume of treatment in men with nutrition, or rather its imbalance and irrationality is obvious. With the increase in the standard of living of the population, the incidence of this disease has also increased – gout has truly been the misfortune of overeating humanity, whereas in third world countries it is quite rare.

Keywords: gout, hyperuricemia, uric acid, allopurinol, meloxicam, treatment, efficacy, safety.

INTRODUCTION

Gout is a systemic tofus disease characterized by the deposition of sodium monaurate (SMU) crystals in organs and tissues in individuals with chronic hyperuricemia and the development of recurrent arthritis caused by external environmental and/or genetic factors.

The development of gout is based on an increase in the concentration of serum uric acid (sSUA) and the subsequent formation of crystals of sodium salt of uric acid.

They are recognized and captured by macrophages, then attacked by neutrophils. The subsequent release of inflammatory mediators provokes the inflammatory process, vasodilation and attraction of immune cells to the focus.

Clinically, gout is manifested by recurrent acute arthritis – pronounced hyperemia, pain and edema, developing within 3-12 hours. During the first 3-5 years, topuses form in patients without treatment, and the disease is considered as chronic. The traditional risk factors, such as male sex, increased life expectancy, metabolic syndrome, the use of diuretics, primarily loop, were added to the intake of low doses of acetylsalicylic acid, cyclosporine and the presence of chronic renal diseases. General practitioners in their medical activities provide first aid in the management of patients with gout, which is a curable disease, but its treatment in most people is still far from optimal. Firstly, insufficient familiarity of a wide range of doctors with the Russian algorithm of management and new clinical recommendations, including the most effective modern methods of treatment and medications. Less than 50% of patients with gout receive therapy that reduces the qMS, and even in this case, the doses of drugs are insufficient to effectively reduce it to the target level. Secondly, methods of unconditional adherence of patients to systematic preventive treatment of chronic disease, and not only relief of acute and exacerbation of chronic joint syndrome, have not been fully developed.

In essence, the diagnosis of gout means the need for lifelong treatment, as is already generally recognized in the management of patients with diabetes, hypertension and other chronic diseases. General principles of patient management include full awareness of the pathophysiology of the disease, lifestyle, availability of effective treatment methods, associated concomitant diseases, principles of treatment of an attack of acute gouty arthritis and prevention aimed at dissolving SMU crystals by continuous lifelong reduction of sSUA and achieving its target level. The target level of qMS should be considered below 6 mg/dl (less than 360 mmol/L), i.e. below the point of supersaturation of SMU, and it is important to maintain it throughout life. In patients with normal renal function, allopurinol is recommended as a 1st-line drug. The starting dose is 100 mg per day with a further increase of 100 mg every 2-4 weeks until the target sSUA level is reached. In patients suffering from renal insufficiency, the dose of allopurinol is selected under the control of creatinine clearance. Treatment for an acute attack of gout includes nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and colchicine. Despite the effectiveness of these methods, 69% of patients experience repeated exacerbations during the year against the background of urate-lowering therapy. Properly carried out prevention of exacerbation of articular syndrome is therefore very important in acute and chronic gout. Preventive therapy of exacerbations of the articular syndrome in gout should be carried out in the first 3-6 months of urate-lowering therapy. Prevention of exacerbations arthritis with colchicine or NSAIDs at a low dose during the first months is more effective than prevention of acute attacks for 8 weeks without increasing the number of adverse events.

In the present study, patients received the original meloxicam to prevent a gout attack. The reason for the choice was the presence of indications in the instructions for the medical use of the drug: treatment of inflammatory arthritis, as well as in accordance with National Recommendations on rheumatology and the widespread use of the drug meloxicam in clinical practice.

The aim of the study was to evaluate the effect of a 12–week course of combined urate-reducing drug therapy 1st-line allopurinol to achieve the target level of uric acid in the blood serum against the background of preventive anti-inflammatory administration of meloxicam on the frequency of exacerbations and quality of life of patients with gout.

MATERIALS AND METHODS

A 12-week observational randomized non-interventional study included 143 patients with a diagnosis of gout, taking into account the clinical recommendations of the Association of Rheumatologists of Uzbekistan, who applied for an outpatient appointment during 1-11 months of 2021. Physical examination was performed on all patients with the calculation of anthropometric data (height, body weight, body mass index), the level of blood pressure (BP) during visits. Clinical blood and urine tests, biochemical blood analysis with determination of the level of qMS, creatinine were performed, C-reactive protein (CRP), instrumental diagnostics (electrocardiography). Information about concomitant diseases was entered, drug therapy was recorded at the time of the program. The diagnosis of arterial hypertension (AH) was established taking into account the European recommendations for the diagnosis and treatment of hypertension (2018), coronary heart disease – based on the European Recommendations for the diagnosis and treatment of chronic coronary syndromes (2021). For the diagnosis of type 2 diabetes mellitus (DM), the criteria of the World Health Organization were used. Chronic kidney disease (CKD) was verified based on the classification of the modern consensus Kidney Disease Improving Global Outcomes (KDIGO) with the calculation of glomerular filtration rate (GFR) using the formula Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI). The diagnosis of chronic venous insufficiency was made in accordance with the criteria of the guidelines for clinical Practice of the European Society of Vascular Surgery (ESVS).

Inclusion criteria: the age of patients from 18 to 65 years and the established diagnosis of gout according to the criteria of the American College of Rheumatology (ACR) and the European League against Rheumatic Diseases (EULAR) from 2015.

Exclusion criteria: if the patient received therapy with any NSAID, as well as intolerance or contraindications to them, patients with secondary gout, the presence of concomitant conditions and diseases, such as uncontrolled diabetes, uncontrolled hypertension, congestive heart failure, peptic ulcer in the acute phase, clinically significant liver and kidney diseases, uncontrolled thyroid dysfunction, non-healing wounds, ulcers, bone fractures, mental illness, uncontrolled epilepsy, narcotic addictions that may endanger the patient's safety or affect the safety assessment of the investigational drug.

Allopurinol was prescribed according to the standard scheme: inside,1 time a day after meals, with plenty of water. Every 3 weeks the dosage of the drug was increased by 50 mg up to a daily dose of 300 mg. Meloxicam is used in the form of 7.5–15 mg tablets, once. A twelve-week course, as well as intramuscular (i / m) administration of the drug are indicated only for 3 days of therapy in the presence of severe pain syndrome, swelling, redness of the joint. The total daily dose of the drug Meloxicam, used in the form of different dosage forms, did not exceed 15 mg. The intensity of joint pain was measured on a visual analog scale – VAS (100 mm): 5-44 mm pain was classified as mild, 45-74 mm – moderate, 75-100 mm – severe. The degree of edema,

soreness, erythema, and the amplitude of movements in the monitored joint were evaluated according to the psychometric Likert scale, when working with which the patient evaluates the degree of his agreement or disagreement with each judgment, from "completely agree" to "completely disagree". To assess the quality of life, the general international questionnaire EuroQol-5D-5L (European Quality of Life Instrument) was used. All indicators were evaluated 3, 6, 9, 12 weeks after the start of the use of the studied drugs. Satisfaction with treatment was assessed on a scale from 1 to 5, where 1 is a complete lack of improvement or deterioration, and 5 is a very good result. The primary endpoint of the effectiveness of therapy was a decrease in the severity of joint pain according to VAS, as well as dynamics on the Likert scale, assessment of the patient's quality of life according to the questionnaire EuroQol-5D-5L. Secondary efficiency endpoints included a decrease compared to the baseline the concentration of uric acid at each visit, as well as compared with the baseline level of the frequency of acute gout attacks. Additionally, the tolerability of combination therapy and the development of adverse events (NS) occurring during the period between the first dose of drugs and 30 days after the last dose of combination therapy were evaluated.

RESULTS

The study included 143 patients with gout (60.1% – men, average age – 60.7±13.4 years, body mass index – 31.8±6.4 kg/m2). The age of patients at the onset of gout was 56 ± 14.3 years, the duration of the disease was 6.1± 2.8 years. Tofuses were diagnosed in 20.3% of cases. The recurrence rate of arthritis over the past year was 3.0 (2.0–5.0) – from 1 to 12 exacerbations, while 93 (65.1%) patients had more than 3 exacerbations per year, 32 (22.4%) had gouty arthritis relapsed every 2 months. Frequency of joint lesions it is shown in the figure (see on the color insert). It was noted that the joints of the lower extremities were more often affected in men, and the upper extremities – in women. The average number of affected joints was 2.8±1.4. Articular syndrome in 7.7% of cases was polyarticular in nature.

The majority of patients had comorbid pathology: hypertension (65.8%), coronary heart disease (41.3%), postinfarction cardiosclerosis/acute cerebral circulation disorder in the anamnesis (33.6%), type 2 diabetes (24.5%), chronic heart failure (22.4%), CKD (39.2%), chronic venous insufficiency (11.9%). The average qMS level at the start of the study was 552.6±96.4 mmol/l.

Stage I of hypertension – in 12.6%, stage II – in 25.9%, stage III – in 27.3% of patients. The duration of the course of hypertension was 7.6 [4; 11] years. Grade 1 hypertension was detected in 11.9%, grade 2 in 23.8%, and grade 3 in 30.1% of patients. Working systolic blood pressure (SAD) averaged 128.6 [120; 130] mmHg; working diastolic blood pressure (DAD) – 80.5 [80; 80] mm Hg. Maximum increase The SAD averaged 174.4 [160; 195], the maximum DAD – 101.6 [90; 101] mmHg. GFR according to the standard calculation method (formula CKD-EPI), it was found that CKD Stage I was diagnosed in 9.1% of patients, stage II CKD – 30.1% according to the standard calculation method (CKD-EPI formula).

Pharmacotherapy of comorbid pathology: 29.4% of patients received antiplatelet agents or anticoagulants, 25.9% – lipid–lowering drugs; 21% – diuretics, 23% – angiotensin converting enzyme inhibitors, 25.2% - angiotensin II receptor blockers, 21% – calcium channel blockers, 40.5% – b-blockers. Patients took drugs systematically in 32.1% of cases, episodically – 25.3%, there was no treatment in 8.4% of patients.

Table 1. Dynamics of the severity of individual characteristics of gouty arthritis

Indicator	1st visit (0 weeks)	2nd visit (3 weeks)	3rd visit (6 weeks)	4th visit (9 weeks)	5th visit* (12 weeks)
VAS, mm	21,8±8,1	33,3±10,4	45,9±16,5	62,1±21,7	23,8±13,4
JOINT SWELLING:					
1 – missing;	100	100	100	90,9	97,9
2 – "light" palpable edema;				8,4	2,1
3 – "moderate" visible edema;					
4 – "heavy", bulging beyond the joint, %				0,7	
DEGREE OF JOINT SORENESS:					
1 – missing;	86,1	80,4	69,9	63,8	90,9
2 – "light" pain when touched;	13,9	19,6	30,1	27,3	9,1
3 – "moderate" pain and flinching;				6,9	
4 – "severe" pain, flinching and twitching of the limb, %				2,0	
THE DEGREE OF ERYTHEMA OF THE JOINT:					
1 – missing;	100	100	100	91,1	99,3
2 –"availability";				8,9	0,7
3 – "impossibility of evaluation", %					
AMPLITUDE OF MOVEMENTS IN THE JOINT:					
1 – normal range;	92,3	90,2	70,7	63,7	90,9
2 – slightly limited range of motion;	7,7	9,8	29,3	24,5	9,1
3 – moderately limited range of motion;				9,8	
4 – very limited range of motion;				2,0	
5 – movement in the joint is impossible, %					
EUROQOL-5D-5L QUESTIONNAIRE					
1 – I have no difficulty walking;	90,2	89,4	71,2	62,2	90,2
2 – I have little difficulty walking;	9,8	10,6	28,8	30,1	9,8
3 – I have moderate difficulty walking;				7,7	
4 – I have great difficulty walking;					
5 – I am unable to walk, %					
SELF-CARE:					
1 – I have no difficulty washing or dressing;	97,9	97,9	75,5	65,1	84,6
2 – I have a little difficulty washing and dressing;	2,1	2,1	24,5	23,6	15,4
3 – I have moderate difficulty washing or dressing;				11,3	
4 – I have great difficulty washing or dressing;					
5 – I am not able to wash or dress myself, %					
HABITUAL DAILY ACTIVITIES:					
1 – my daily activities are given to me without difficulty;	92,2	92,2	82,5	59,4	89,4
2 – my daily activities are a little difficult for me;	7,8	7,8	17,5	27,3	10,6
3 – my daily activities are moderately difficult for me;				10,6	
4 – my daily activities are very difficult for me;				2,7	
5 – I am not able to do my usual daily activities, %					
PAIN/DISCOMFORT:					
1 – I have no pain or discomfort;	88,1	77,0	67,2	62,3	86,1
2 – I am experiencing a little pain or discomfort;	11,9	23,0	32,8	25,9	13,9
3 – I experience moderate pain or discomfort;				9,1	
4 – I am experiencing severe pain or discomfort;				2,7	
5 – I am experiencing extremely severe pain or discomfort, %					
ANXIETY/DEPRESSION:					
1 – I don't experience anxiety and depression;	81,8	83,9	74,2	53,9	90,9

2 – I am experiencing a little anxiety and depression;	18,2	8,4	11,3	34,3	8,4
3 – I experience moderate anxiety and depression;		7,7	13,1	4,9	0,7
4 – I am experiencing severe anxiety and depression,			1,4	4,9	
5 – I am experiencing extremely severe anxiety and depression, %					
Your health status today, points	97,4 [100;100]	94,4 [100;100]	74,2 [0;95]	45,6 [0;100]	98 [0;100]
SATISFACTION WITH TREATMENT, %					
1					
2					
3				7,7	0,7
4		5,6	19,6	31,5	8,4
5		94,4	80,4	60,8	90,9

The effect of therapy on individual symptoms of gout is presented in Table. 1. The overall assessment of the severity of pain at the first two visits (0-3 weeks) was weak, there was no swelling and erythema of the joints. Analysis of the first part of the EuroQol-5D-5L questionnaire showed that in the "mobility" category, mostly patients noted that they did not experience any difficulties when walking; in the "self-care" category, problems were also absent in most patients; in the "habitual daily activity" category, a significant part of patients were given daily activities without labor. "Pain/ discomfort" – a slight pain syndrome or discomfort increased in 32.8% of the subjects by the 3rd visit. A small "anxiety/depression" was detected already on on the 1st visit, and by the time of the 3rd visit, 13.1% of patients began to experience a moderate degree of these disorders, and 1.4% of patients anxiety has grown to a strong degree. In the second part of the questionnaire, an assessment of the patient's general health was carried out, where it is possible to trace the dynamics of the decline in indicators during 3 visits. As drug therapy, patients took allopurinol with a gradual increase in the dose every 3 weeks by 50 mg and to on the 3rd visit (6th week), and it was 200 mg per day,
Movalis 7.5 mg per day. By the time of the 4th visit (Week 9) exacerbation of arthritis developed in 13 (9.1%) patients. The severity of pain has increased, according to patients, YOUR increased to 62.1 ± 21.7 mm. According to the Likert school, weakly palpable edema appeared in 8.4%, "severe" edema with swelling beyond the joint – in 0.7% of patients; erythema occurred in 8.9% of the subjects; 27.3% had "mild" pain when touched, 6.9% experienced moderate pain and flinching when touched, 2.0% developed "severe" pain, flinching and twitching of the limb; 24.5% had a slightly limited range of movements, 9.8% had a moderately limited range of movements, 2.0% had a severely limited range of movements. Analysis of the first part of the EuroQol-5D-5L questionnaire showed that in the "mobility" category, 30.1% of patients experienced minor difficulties when walking, 7.7% of patients experienced moderate difficulties when walking. In the "self-care" category, 23.6% had minor difficulties with washing and dressing, experienced moderate difficulties with washing or dressing 11.3% of patients. In the category of "habitual daily activities", the distribution of patients experiencing difficulties is as follows: 27.3% – slightly difficult, 10.6% – moderately difficult, for 2.7% – very difficult. Category "pain/discomfort": a slight pain syndrome was present in 25.9%, moderate pain or discomfort – in 9.1%, severe pain or discomfort was experienced by 2.7% of patients. In the

"anxiety/depression" category, 34.3% of patients had a small degree of the indicator, moderate and severe anxiety/depression were experienced in equal proportions by 9.8% of the observed. According to the second part of the questionnaire, the general state of health has noticeably decreased. The dose of allopurinol was 250 mg. In patients with severe pain syndrome, edema, redness of the joint, Meloxicam 15 mg / 1.5 ml was administered intravenously for 3 days, with a positive effect: relief of a gouty attack; further treatment continued with the use of oral dosage forms of meloxicam 15 mg per day for 10 days, followed by a transition to oral administration of 7.5 mg per day. At the moment on the 5th final visit after 12 weeks, the severity of pain returned to the minimum values according to VAS, about 90% of patients according to the EuroQol-5D-5L questionnaire did not experience any difficulties. The dose of allopurinol reached 300 mg per day, meloxicam 7.5 mg per day. Statistical differences were revealed between the severity of the characteristics of gouty arthritis at the time of the 4th and 5th visits ($p<0.05$). By the end of therapy, there was a marked decrease in pain, normalization of the range of movements, an increase in habitual daily activity, self-care, a decrease in the level of anxiety and depression, improvement of general health. The vast majority of patients gave a high – good or very good – assessment of the therapeutic effect of the combination
of drugs. An unsatisfactory response to treatment was noted in one (0.7%) patient due to the inability to stop the developed acute attack of gouty arthritis by taking NSAIDs, therefore, a glucocorticoid was intraarticularly injected into the area of the right knee joint.

The tolerability of the combination of drugs was good, none of the patients developed serious NS. During treatment, blood pressure indicators were in average values: SAD – 132.1 [129; 154] mmHg, DAD – 78.6 [74.4; 91] mmHg, no adverse events from the gastrointestinal tract were noted. NYA was registered in only
one patient (0.7%) during the 2nd visit (week 3) - there was a skin allergic reaction by the type of urticaria, which required taking antihistamines, which allowed to eliminate the manifestations of an allergic reaction and safely complete the full course of treatment without any negative consequences.

The data of laboratory research methods obtained during the examination of patients for 12 weeks are shown in Table. 2. The average level of qMS in the blood varied above normal, but by the 5th visit it reached 413±96.5 mmol/l, but not the target level of qMS. There was a slightly acidic reaction of urine at all visits – pH from 5.0–6.0. The correlation between the severity of certain characteristics of gouty arthritis, taking into account anamnesis, physical examination, questionnaires, laboratory examination methods is presented in Table. 3. The presence of joint edema it is interconnected by direct dependence with the intensity of pain, discomfort and the parameters of the EuroQol-5D-5L questionnaire: joint mobility, pain and inverse dependence with the assessment of the patient's health status. The presence of joint soreness is directly related to the intensity of pain according to VAS ($r=0.31$), the parameters of the EuroQol-5D-5L questionnaire and other indicators. In addition, positive associations of acute phase indicators of ESR and CRP with the age of gout onset and assessment of the patient's health status, as well as the level of qMS with the tofus form of the disease were revealed.

CONCLUSION

The data obtained show the high effectiveness of combined urate-reducing therapy with allopurinol against the background of preventive anti-inflammatory administration of the drug meloxicam in 90% of patients participating in the study, who at the end of the treatment course rated the combined effect as good (8.4%) or
very good (90.9%). Against the background of treatment with meloxicam, more than 2/3 of patients did not have a worsening of the articular syndrome with an increase in the dose of allopurinol. And by the 12th week, a significant difference was revealed between the severity of the indicators of the joint syndrome of gouty arthritis in the direction of improvement. In addition, the levels of ESR and qMS were significantly different at the beginning and at the end of the observation, which indicates a positive effect on the inflammatory process. In 90.9% of cases, we achieved the target qMS level. Not all patients received a good response to therapy. By the 4th visit, 13 (9.1%) patients had a recurrence of an attack of gouty arthritis, which required switching to the IV route of administration of meloxicam and one patient had a local injection of glucocorticoids. It should be noted that this study was conducted among patients who had more than 3 exacerbations per year and the dose of allopurinol was constantly increasing, and at the 4th visit it was 250 mg. Taking into account the data obtained, the frequency of acute attacks of gout decreased by 2.5 times compared to the baseline level, and the combined intake of urate-lowering therapy with allopurinol and a prophylactic dose of the anti-inflammatory drug meloxicam was well tolerated, was not accompanied by significant increases in blood pressure, changes in creatinine clearance, urea in blood serum. There were no adverse events from the gastrointestinal tract.

The results obtained to assess the relationship between the severity of the characteristics of gouty arthritis, laboratory data and quality of life assessment showed that the intensity of clinical manifestations of an acute attack of gout, as well as acute phase indicators, weakly correlated with the age of gout onset, the duration of the disease and the presence of tofuses, but significantly correlated with the intensity of pain syndrome, restriction of daily activity, the possibility of self-care, the presence of anxiety and depression.

The data obtained by us confirm the good therapeutic effect and favorable tolerability of combined urate-reducing therapy with allopurinol against the background of preventive anti-inflammatory administration of Meloxicam. Analysis of the results of the study showed the rapid anti-inflammatory and analgesic effect of meloxicam, its positive effect on all clinical manifestations of gouty arthritis. Undoubtedly, with the introduction into practice of combined urate-reducing therapy with allopurinol against the background of preventive anti-inflammatory administration of meloxicam in doctors have a new, convenient and effective tool for monitoring the course of gouty arthritis.

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