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THE EFFECT OF URATE-REDUCING THERAPY ON THE INDICATORS QUALITY OF LIFE IN PATIENTS WITH GOUT

Khusainova Munira Alisherovna
Yarmatov Suvon Totlibayevich
Ergashova Ma'mura Toshtemirovna
Gafforov Xudoyor Xudoyberdiyevich
Samarkand State Medical University

ABSTRACT

Gout can have a significant impact on the quality of life (QOL) of patients.

The aim of the study was to evaluate the dynamics of QOL indicators and the possibility of achieving the target level of uric acid (UA) in gout patients with inefficiency and/or contraindications to the appointment of allopurinol receiving febuxostat.

Patients and methods. A prospective single-center study included 80 patients diagnosed with gout. The observation period was at least 6 months of the use of allopurinol or febuxostat in doses necessary to achieve the target level of UA.

At the initiation of urate-lowering therapy, allopurinol 100 mg/day was prescribed, followed by titration of the dose (up to a maximum of 900 mg/day) until the target level of MC (<360 mmol/ L) was reached. Patients with inefficiency of allopurinol and/or the presence of adverse reactions (AR) were transferred to febuxostat 80-120 mg/day.

All patients received low doses of nonsteroidal anti-inflammatory drugs or colchicine 0.5 mg/day or glucocorticoids 7.5 mg/day in terms of prednisone for the prevention of arthritis attacks. At the first and last visits, patients who were treated with febuxostat filled out the SF-36 questionnaire.

Results and discussion. After 6 months of follow-up, 70 (88%) patients received urate-lowering therapy, of which 51 (73%) reached the target UA level. Titration of the dose of allopurinol was required in 26 patients, of which 14 (54%) achieved the goal of treatment.

Due to the ineffectiveness of allopurinol, 32 patients were switched to febuxostat, which in 69% of cases allowed normouricemia to be achieved. In 15 (68%) of 22 patients who were initiated therapy with febuxostat due to the presence of AR on allopurinol, the target level of UA is also fixed. In patients who received febuxostat and reached the target level of UA, QL indicators improved: role functioning due to physical condition, pain intensity, general health, vital activity and general physical well-being ($p<0.05$ in all cases). In patients who did not reach the target UA level

when taking febuxostat, such indicators as physical functioning, role-based functioning due to physical condition, and others improved- pain intensity ($p<0.05$ in all cases). High adherence to therapy was observed in 63% of patients receiving febuksostat, and in 36% – allopurinol.
Conclusion. In patients with inefficiency or intolerance to allopurinol, febuxostat administration in 69% of cases allows achieving the target level of MC, as well as improving QL and adherence to therapy.

Keywords: gout; quality of life; urate-lowering therapy; febuxostat

Gout is the most common form of arthritis, significantly impairing the function of joints and the quality of life (QOL) of patients. The deterioration of QOL in gout is associated with both the features of its clinical manifestations (acute excruciatingly painful attacks of arthritis, the formation of bone destruction, subcutaneous and intra-tissue topuses, concomitant diseases, including damage to the cardiovascular system and kidneys, metabolic syndrome and its components), and socio-demographic factors (age, gender, index body mass – BMI – etc.). Gout affects many aspects of the patient's life, limiting his daily and professional activities during seizures, causing significant stigmatization and guilt for the development of exacerbations, which leads to masking pain and hiding the symptoms and consequences of the disease, as well as depression, the prevalence of which in such patients ranges from 13.5 to 20%. Since gout is often associated with comorbid conditions, it is not always clear what is the main cause of QOL deterioration. In addition, it is important to understand what the effect of treatment on QOL is. Despite the availability of urate-lowering drugs, in many patients it is not possible to achieve the target level of UA in serum blood, including due to poor adherence to therapy. According to most studies, high compliance and satisfaction with treatment positively correlated with QOL. At the same time, there are opposite results indicating that allopurinol did not improve QOL indicators related to physical health. One of the ways to increase adherence to therapy for gout and reduce the fear of exacerbation is strict medical supervision, patient education, and the use of the most effective treatment methods, including urate-lowering and anti-inflammatory drugs that have a convenient intake regimen. Gout can be completely controlled if the target level of UA in the blood serum, which should be <360 mmol/l, is reached and maintained. Despite the introduction of the "Treatment to Goal" strategy, some patients still have unsatisfactory therapy results. So, in the French cohort of patients with gout, in the first year of treatment, the target level is UA in blood serum was achieved in about a

quarter of patients, and in the UA over the same period – only in a third. It was found that in the absence of gout control QOL in patients becomes worse than in the population. At the same time, it is unclear whether it is possible to improve the quality of life in patients who are fully or partially resistant to our lowest therapy, in whom the serum level of UA exceeds the target even when using maximum doses of drugs.
The purpose of the study is to assess the dynamics of indicators QOL and the possibility of achieving the target level of UA in patients with gout with inefficiency and/or contraindications to the appointment of allopurinol receiving febuxostat.

MATERIALS AND METHODS

This work was carried out within the framework of a "Single–center open prospective study of the effect of combined urate-lowering (febuxostat - in comparison with allopurinol) and anti-inflammatory therapy on QOL, the risk of developing arthritis attacks and the level of uricemia in patients with gout in clinical practice". Inclusion criteria: patients of both sexes over the age of 18 with an established diagnosis of gout (classification criteria of the American College of Rheumatology / European Alliance of Associations for Rheumatology, ACR/EULAR 2015); patients both in the absence and on the background of treatment with allopurinol who did not reach the target level of MC (<360 mmol/l; for patients with severe tofus gout <300 mmol/l); signed informed consent form. Non-inclusion criteria: the presence of contraindications listed in the instructions for the medical use of febuxostat and allopurinol; uncontrolled arterial hypertension (AH), chronic heart failure (CHF) ≥stage III according to NYHA, coronary heart disease (angina pectoris, postinfarction cardiosclerosis, painless myocardial ischemia, ischemic cardiomyopathy), surgery on heart (coronary artery bypass grafting, endovascular stenting, etc.), ischemic stroke; transient ischemic attack; glomerular filtration rate (GFR) <30 ml/min (formula CKD-EPI); increased levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2 norm; uncompensated diabetes mellitus (DM; serum the level of glycated hemoglobin – HbA1c > 7%); the presence of somatic or mental diseases that prevent the implementation of research procedures; simultaneous participation of the patient in any other clinical study. When initiating urate-lowering therapy, allopurinol was used at a starting dose of 100 mg/day, followed by its increase by 100 mg/day every 2-3 weeks until the target level of UA (<360 mmol/L) was reached, up to a maximum of 900 mg/day, and in patients with GFR <60 ml/min /1.73 m^2 – up to 300 mg/day.
Patients who have not experienced a decrease in the level of UA when using the maximum possible doses of allopurinol and / or there were adverse reactions

associated with it (HP), including according to anamnesis, febuxostat was prescribed at an initial dose of 80 mg / day, which was increased to 120 mg / day if necessary. The follow-up period for each patient covered at least 6 months of continuous use of febuxostat. After screening and inclusion in the study, scheduled visits took place on the 14th day, 3 and 6 months after the start of urate-lowering therapy. Patients receiving allopurinol additionally visited a doctor every 2 weeks in order to titrate the dose of the drug.

To prevent attacks of acute arthritis, standard anti-inflammatory therapy was prescribed, which included one of the nonsteroidal anti-inflammatory drugs (NSAIDs) in minimal therapeutic doses or colchicine 0.5 mg/day, and if they are intolerant or there are contraindications – glucocorticoids (GC) 7.5 mg/day in terms of prednisone. The choice of a specific drug was carried out individually.

During the first and last (after 6 months) visits, all patients, including those who received febuxostat, filled out a questionnaire, the SF-36 questionnaire, containing 36 questions about the state of health, grouped into 8 scales, which form two indicators – the "physical component of health" and the "psychological component of health", in order to assess the indicators of QOL. Adherence to therapy was assessed using the Morisky–Green questionnaire.

Arthritis was detected either by the doctor during the visit, or by the patient himself using a validated questionnaire for determining exacerbation in patients with established gout, including four criteria: the presence of arthritis according to the patient; pain at rest > 3 points on a numerical evaluation scale (0-10 points); the presence of 1 swollen joint; the presence of 1 warm joint. An attack of arthritis was recorded in the presence of ≥3 criteria.

Assessment of cardiovascular safety against the background of febuxostat treatment was carried out by monitoring the occurrence and/or evolution of complaints in accordance with the recommendations of Food and Drug Administration. During the visits, mandatory laboratory tests were performed to assess the effectiveness and tolerability of therapy: a general blood test, a general urine test, determination of the level of MC, glucose, ALT, AST, creatinine, creatine phosphokinase (CPK). The study of HbA1c and CRP was carried out at the first and last visits.

Statistical analysis was carried out using the Statistica 12.0 application software package (StatSoft Inc., USA) of descriptive statistics. The results are presented in the form of mean values and mean quadratic deviations (M ±SD) for quantitative features having a normal distribution, in other cases – in the form of median and interquartile interval (Me [25th; 75th percentile]). In the process of statistical data processing, descriptive statistics methods were used to compare two independent groups on a

quantitative basis – the Mann–Whitney criterion. The differences were considered significant at $p<0.05$.

RESULTS

After 6 months of follow-up, 70 (88%) of 80 patients received urate-lowering therapy, of which 51 (73%) had a target level of UA. Titration of the dose of allopurinol was performed in 26 patients, of which 14 (54%) reached the target level UA. During the follow–up, the development of HP was registered in 2 patients receiving allopurinol: one had an increase in serum creatinine level to 160 mmol/l and a decrease in GFR to 36.7 ml/min/1.73 m^2 and later to <30 ml/min/1.73 m^2 , the other had a three–fold increase serum levels of ALT and AST. Two (2.5%) patients did not show up for final visits, and it was not possible to establish feedback with them.

At the time of inclusion in the study, 32 patients from- the ineffectiveness of allopurinol in the maximum permissible doses was noted, and therefore febuxostat was prescribed to them. Of these, 22 (69%) patients reached the target UA level. HP in the form of urticaria was noted in 1 case. According to the anamnesis, 22 patients had poor tolerance of allopurinol: itching of the skin – in 10, urticaria – in 9 and a more than twofold increase in the level of hepatic transaminases – in 3. He also initiated febuxostat therapy, against which 15 (68%) patients had a target level of UA. HP developed in 3 patients: in 2 – a more than twofold increase in the level of ALT and AST, in 1 - an increase in the serum level of CPK to 547.8 mmol / l and AST to 40.7 units / l (this patient received for the prevention of arthritis attacks NSAIDs). Among the patients who used febuxostat, only 2 refused to take the drug. Of the 48 patients who completed the study, 21 took febuxostat at a dose of 80 mg / day, and 27 – at a dose of 120 mg / day.

All patients were prescribed prophylactic anti–inflammatory therapy: NSAIDs - 13 (16%), colchicine – 58 (73%), GC - 9 (11%;). In 49% of cases, there were no exacerbations of arthritis.

Of the 38 patients who had subcutaneous tofuses, 21 (55%) had a statistically significant decrease in them ($p<0.05$), 19 of these patients received febuxostat and 2 – allopurinol; another 2 (5%) patients with febuxostat therapy showed a complete regression of tofuses.

QL was assessed using the SF-36 questionnaire in 48 patients, of whom 37 reached and 11 did not reach the target MC level after 6 months of taking febuxostat.

After 6 months of treatment with febuxostat, patients who had a target level of MC had an improvement in QL according to the following scales: "role functioning due to

physical condition", "pain intensity", "general health", "vital activity and general physical well-being" compared with baseline indicators ($p<0.05$ in in all cases).

In patients of the febuxostat group who did not reach the target level of MC, there was also an improvement in QL on the scales: "physical functioning", "role-playing functioning due to physical condition" and "pain intensity" ($p<0.05$). According to dynamic observation, after 6 months of therapy, the indicator of general health was statistically significantly higher in those who reached the target level of MC than in those who did not reach the treatment goal ($p<0.01$).

During the last visit, 70 patients were It is proposed to take the Morisky–Green test to assess adherence to therapy. The test results showed that adherence to therapy was statistically significantly higher ($p=0.04$) in patients receiving febuxostat compared to with patients taking allopurinol: 30 (63%) out of 48 versus 8 (36%) out of 22. When analyzing the safety of febuxostat, no cases of complaints from the outside were found in our patients cardiovascular system (chest pain, feeling of lack of air, shortness of breath with little physical exertion or at rest, frequent or irregular heartbeat, numbness or weakness in one half of the body or limb, dizziness).

DISCUSSION and CONCLUSION

Previously, it was found that the QOL indicators in patients with gout are significantly inferior to the population ones. At the same time, the deterioration mainly concerns physical health and, to a lesser extent, psychological state (decreased social adaptation).

Although none of the tools used to assess QOL covers all clinical manifestations of gout, it was the SF-36 questionnaire that was proposed to characterize QL in dynamics during clinical trials in such patients. One of the arguments in favor of using this questionnaire for gout was the possibility of a separate assessment of the physical and mental components QOL, since patients with gout suffer more from physical health. In addition, SF-36 has an advantage in cases of a combination of several somatic diseases, which is especially important in gout.

Adherence to therapy and the number of patients, about- the proper intake of febuxostat in our study was high: after 6 months of follow-up, 88% of patients received urate-lowering therapy, the target level UA reached 73%, which is higher than in previously published works. So, according to a number of European and American studies, only 50% of patients did not miss scheduled control visits, only 25-50% reached the target level of UA. The differences obtained are probably related to stricter control and constant monitoring of patients in our study. In our earlier study, which examined adherence to treatment in compliance with national guidelines for the

management of patients with gout, high compliance was detected in 49% of cases. At the same time in the group febuxostat followed the doctor's recommendations of more than half of the patients, whereas in the allopurinol group – only 40%. In this study, 63% of patients receiving febuxostat demonstrated high adherence to therapy, and only 36% – allopurinol.

It is important that the reason for switching patients from allopurinol to febuxostat did not affect the achievement of the target level of UA: in 69 and 68% of patients, respectively, with inefficiency and intolerance to allopurinol, the goal of therapy was achieved. Taking febuxostat contributed to a decrease in the level of UA to the target in almost 70% of cases, which is consistent with the results of previously published clinical studies.

The only parameters of QL that, despite achieving the target level of UA, remained unchanged, were role functioning and mental health. Previous studies have found that, in general, mental health indicators in patients with gout are similar to those in general population, but with severe gout they are lower than in patients with a target level of UA. Interestingly, in our study, an improvement in a number of QOL indicators was also noted in patients who did not there was a decrease in the level of UA: as in patients who achieved the goal of therapy, their pain intensity decreased ($p=0.02$). Given that the relationship between the level of UA and the frequency of gout attacks is almost linear, it can be assumed that a decrease in the level of UA even in the absence of achieving the target level will be accompanied by a decrease in the frequency of exacerbations of arthritis, and consequently, the improvement of quality of life. A. Shoji et al. it was found that with an average concentration of UA in blood serum <360 mmol/l in 86% of cases for 3 years after there were no repeated gout attacks after the first doctor's consultation. Thus, in patients with inefficiency or intolerance to allopurinol, taking febuxostat contributes to achieving and maintaining the target level of UA, improving QL indicators and adherence to therapy.

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