

G.O. Protsenko

K.A. Ivanova

SI "NSC" Institute of Cardiology named after M.D. Strazhesko of NAMS of Ukraine"

Keywords: osteoarthritis, synovitis, dyslipidemia, treatment.

THE USE OF FIBRATES IN PATIENTS WITH OSTEOARTHRITIS WITH CONCOMITANT DYSLIPIDEMIA

Based on clinical and instrumental examination, an analyzes of complex treatment of osteoarthritis of the knee joints in patients with synovitis and dyslipidemia has been carried out, which leads to correction of lipid metabolism and reduces the activity of inflammation.

INTRODUCTION

Osteoarthritis (OA) is a heterogeneous group of diseases of different etiologies with similar biological, morphological, clinical manifestations, which are based on destruction of all components of the joint: cartilage, subchondral bone, synovium, ligaments, capsule and periarticular muscles [4, 5]. Management of patients with OA is challenging and requires a comprehensive approach in choosing a method of treatment that is determined by several factors, among which the basic importance has the severity of pain and inflammatory response, functional failure, the degree of structural change, age and presence of comorbidities.

The important role of the inflammatory component in OA progression is demonstrated by terminology - abroad this disease is called "osteoarthritis", - unlike "osteoarthrosis" - the term adopted in Ukraine [9, 12]. Local inflammation in OA or development of secondary synovitis determines the severity of pain in OA patients and determines their quality of life. Expression of a wide range of inflammatory mediators contributes to the progression of the disease. Development of catabolic processes in cartilage in OA is associated with increased activity of pro-inflammatory cytokines interleukin (IL) -1 and -6, tumor necrosis factor (TNF)- α . It is known that TNF- α and IL-6 stimulate chondrocytes, leading to increased synthesis of proteases. Chondrocytes that regulate remodelling of cartilage, under the influence of cytokines synthesize proteolytic enzymes, which, in turn, cause the degradation of collagen and proteoglycan of cartilage. IL-6 has a special role in the inflammatory response at OA. This neurotransmitter is associated with increase of number of monocytes, macrophages in the synovial membrane, proliferation of chondrocytes and enhance the effect of IL-1 to increase the synthesis of metalloproteinases (MMPs), and inhibition of proteoglycan synthesis [3]. Proinflammatory IL-6 activates the nuclear factor kappa B (NF- κ B), available in different types of cells, including the cells of the synovial of joints. Its role in development of OA is obviously realized by influencing proinflammatory and anabolic cytokines, which, in turn, affect the metabolism of cartilage [1, 6].

Effect of IL-6 on lipid metabolism is manifested in reduced concentrations of apolipoproteins (apo)-A1, A2, B, cholesterol level by reducing the concentration of high density lipoproteins (HDL) and low density lipoproteins (LDL), increased triglycerides (TG) [12]. Relationship between levels of C-reactive protein (CRP), cytokines (IL-6, TNF- α), cell adhesion molecules and lipid profile indicators confirms the concept of chronic inflammation in the development of dyslipidemia [10, 12]. In the study of comorbidity in OA patients, prevalence of cardiovascular disease (80%), including high spread of lipid metabolism failure – dyslipidemia was observed, which worsens the prognosis in these patients. Individuals with OA have higher cardiometabolic risk through forming a group of factors - reduced HDL cholesterol, increased triglycerides, CRP [3]. Lipid metabolism failure, including the option of atherogenic dyslipidemia, the components of which is increasing the TG, increased lipoprotein cholesterol content of very low density (VLDL), decreased HDL, is complex, a special role is allocated to macrophages that produce cytokines (IL-6, TNF - α) [11].

For a long time the only drugs for the treatment of OA remained analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs). However, a significant number of side effects from the gastrointestinal tract and the cardiovascular system limits their widespread use, especially in older age groups. European, American management recommend the use of NSAIDs at the lowest effective doses and if possible – in short courses [2, 4]. For a long time OA was regarded as an isolated disease of the joints associated with the degeneration of cartilage. Today specialists believe that the basis of the progression of OA is a lot of interconnected to each other causes and mechanisms, including genetic predisposition, biomechanical and metabolic changes, local inflammation and more.

Lipid-lowering drugs such as fibrates - derivatives of fibric acid may reduce levels of some inflammatory markers, including CRP, IL-6 and fibrinogen, which leads to their prescription to patients with OA and synovitis and concomitant diseases of the cardiovascular system [7].

The objective of this research is to assess the efficacy and safety of fibrates in patients with knee OA with synovitis and dyslipidemia.

OBJECTS AND METHODS OF RESEARCH

Evaluation of clinical efficacy of fenofibrate was conducted on the basis of department of non-coronarogenic heart diseases and clinical rheumatology of SI "NSC" Institute of Cardiology named after M.D. Strazhesko of NAMS of Ukraine". The study involved 50 patients with knee OA with synovitis in the age of $56,62 \pm 1,46$ years, of which 13 (26%) were men, 37 (74%) were women. All patients were divided into two groups: the 1st group - 20 OA patients with a primary lesion of the knee joints with the presence of synovitis and concomitant dyslipidemia; and the 2nd group - 30 patients with OA with a primary lesion of the knee joints with the presence of synovitis, without lipid metabolism failure.

Group 1 contained 4 (20%) men and 16 (80%) women, mean age $57,85 \pm 2,37$ years old. All patients of Group 1 received fenofibrate in the recommended dose of 250 mg/day (1 capsule in the evening). Duration of treatment was 1 month. The drug was prescribed in accordance with the manufacturer's recommendations in accordance with doses as in instructions. All patients with

pain were taking NSAIDs (diclofenac 50 mg 2 times a day) in short-courses (1 week) at the beginning of treatment.

Group 2 contained 9 (30%) men and 21 (70%) women, mean age $55,8 \pm 1,9$ years old. All patients in Group 2 received NSAIDs (diclofenac 50 mg 2 times a day) for 1 month. In addition, all patients from the 1-st and the 2-nd group took chondroprotectors (chondroitin sulfate 500 mg 2 times a day). The surveyed from the 1st group continued to receive the usual treatment, depending on comorbidities: 14 people had hypertension (average blood pressure 165/95 mm Hg.) and 1 patient had diabetes mellitus type II. Since the patients of group 1 were overweight (body mass index in the group averaged $29,06 \pm 1,24$) and concomitant dyslipidemia, a diet with reduced fat and carbohydrates was recommended.

Thus, as can be seen from Table. 1, all surveyed of the 1-st and the 2-nd groups on average almost did not differ by age and disease duration.

Table 1

General characteristics of patients

Indicator	1st group	2nd group
Age, years	$57,85 \pm 2,37$	$55,8 \pm 1,9$
Gender:	20	30
men, n (%)	4 (20)	9 (30)
women, n (%)	16 (80)	21 (70)
Duration of disease, years	$7,4 \pm 1,02$	$7,9 \pm 1,9$
Radiological stage :		
I, n (%)	2 (10)	0
II, n (%)	17 (85)	21 (70)
III, n (%)	1 (5)	9 (30)

However, participants in group 2 had pronounced manifestations of OA: in 21 patients - radiological stage II, and in 9 patients – stage III vs. 17 patients of group 1 with radiological stage II and 1 person – with stage III.

The basis of the analysis was rating the severity of gonarthrosis acc. to index M. Lequesne (1999): (1-4 - weak, 5-7 - average, 8-10 – expressed, 11-13 - significantly expressed, > 14 – strongly expressed). The range of motion in the knee joints was determined using a goniometer by a neutral null method.

Also pain, articular, inflammatory indices analysis was carried out. Articular index was determined by the severity of pain on palpation of the joints: 0 points - joint insensitive, 1 point - slight pain, 2 points - moderate pain, 3 points - severe pain. Inflammatory index was determined according to manifestations of exudative inflammatory changes of a joint: 0 points - exudate is absent, 1 point - a little exudate, 2 points - moderate exudate, 3 points - much more expressed exudation. Pain index was measured with active and passive movements of the joints: 0 points - no

pain, 1 point - a little pain, 2 points - moderate pain, 3 points - intense pain (movement sharply limited or impossible).

The evaluation was performed by visual pain scale - VPS (100 mm), morning stiffness was also assessed, as well as synovitis laboratory activity analysis (erythrocyte sedimentation rate (ESR), CRP), except that in the patients of group 1 TNF- α , IL- 6 («ProCon», Russia) was additionally measured, which were evaluated by ELISA method. Indicators of lipid profile were determined using standard accepted method.

The key moment in determining the effectiveness of anti-inflammatory effect of the complex treatment was ultrasonography (USG) of joints before and 1 month after the treatment. Ultrasonography of joints was performed at device "SONOLINE Omnia" (Siemens) with a linear sensor 7,5 L70 (frequency of 7.5 MHz) in "ortho" mode, and for each of the estimated joint standard sensor positioning was used. Bone articular surfaces were evaluated (subchondral bone surface changes - the presence of cysts, erosions and other defects), joint cracks, synovial membrane, soft tissues around joints, the presence of effusion, changes of ligaments and some other parameters [5].

Synovitis most often occurs in suprapatellar space of a knee joint (upper twisting). Suprapatellar bag is the largest in the human body and extends 6 cm up proximal to the upper pole of a patella. Any impact on a knee joint (inflammatory, traumatic) leads to increased amounts of synovial fluid in the upper joint twisting [8].

Analysis of clinical and laboratory parameters of the patient was performed before the trial and 1 month after treatment.

Rate of overall effectiveness of treatment was evaluated using the following scale: significant improvement - 2 points, improvement - 1 point, no change - 0 points, deterioration - 1 point.

Tolerability of treatment was evaluated as "good" (2 points), "satisfactory" (1 point) and "unsatisfactory" (0 points). Statistical processing of the results was performed on a personal computer using standard statistical software "Microsoft Exel", Windows 2000. Mean arithmetic value (M) was calculated, as well as standard deviation (σ), and Student's t-criterion.

EVALUATION OF RESULTS

According to ultrasound research (Table 2), at baseline, all patients had evidence of synovitis (presence of effusion in the joint cavity - 50 people). Thus, the role of the inflammatory component in OA is confirmed, according to instrumental investigation (USI).

Table 2

Ultrasound monitoring survey data in OA patients
before and after treatment

Indicator	1st group		2nd group	
	Before treatment	After treatment	Before treatment	After treatment
USI data: presence of synovitis:	20	11	30	18

- Unilateral, n (%)	7 (35)	6 (30)	19 (63,3)	15 (50)
- Bilateral, n (%)	13 (65)	5 (25)	11 (36,6)	3 (10)

Thus, a positive trend in reducing the signs of synovitis in both groups was present. Also the dynamics of the upper torsion effusion of the knee was evaluated (Fig.1). In group 1 effusion decreased by an average of 28.75 ml (35%) in the 2nd group - overall effusion decrease was in general 25.1 ml (68.6%).

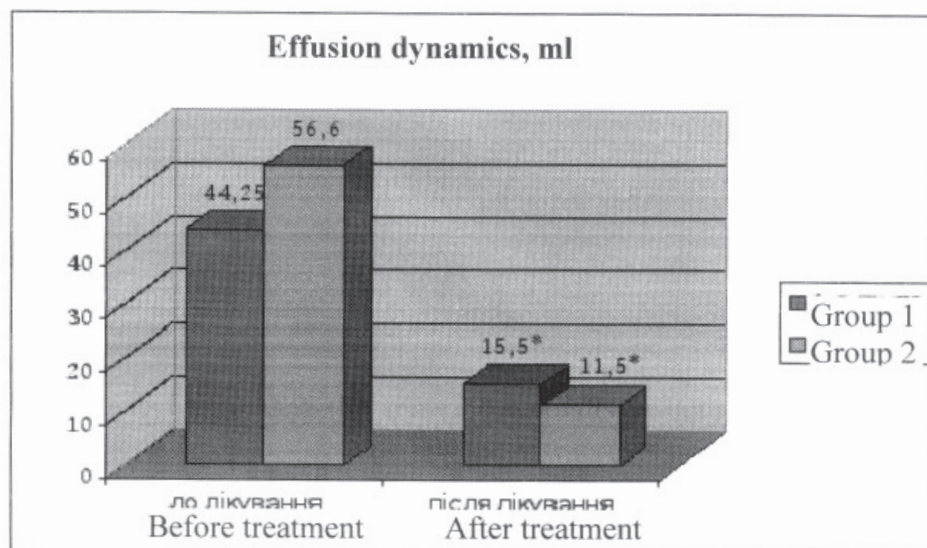


Fig. 1. Dynamics of effusion (ml) of knee joints in the upper twisting. In Fig. 1-4: *p < 0.05 between groups before and after treatment

The therapy helped to change the severity of gonarthrosis before and after treatment.

Table 3

Assessment of gonarthrosis severity according to M. Lequesne index

Severity	1st group		2nd group	
	Before treatment	After treatment	Before treatment	After treatment
Slight (1-4)	n=0	n=12	n=0	n=1
Average (5-7)	n=7	n=4	n=8	n=16
Expressed (8-10)	n=5	n=3	n=11	n=13
Significantly expressed (11-13)	n=3	n=1	n=7	n=0
Acute (> 14)	n=5	n=0	n=4	n=0
Average rate	10,5±1,11	5,33*±0,72	10,03±3,06	7,1±1,6

In Table 3-6: * p<0.05 between groups before and after treatment.

Assessment of the dynamics of gonarthrosis severity according to M. Lequesne index (Table 3) showed that in patients of group 2 before treatment there prevailed average and expressed severity of gonarthrosis, as well as significantly expressed, but generally it decreased by 49.2% in group 1 and 29.2% in group 2.

Articular status and its dynamics during treatment were assessed according to pain, joint, inflammatory indices (Table 4), as well as the local status of joints.

Table 4

Assessment of the indices dynamics

Index (average Indicator)	1st group		2nd group	
	Before treatment	After treatment	Before treatment	After treatment
Pain	1,65±0,11	0,75*±0,13	2,03±0,4	0,9*±0,5
Articular	1,5±0,14	0,4*±0,12	1,3±0,5	0,3*±0,4
Inflammatory	1,35±0,15	0,35*±0,11	1,4±0,6	0,3*±0,4

Thus, pain index was higher in group 2 before treatment and generally decreased by 1.13 (55.7%), in group 1 it decreased by 0.9 (54.5%). The articular index dynamics was as follows: it decreased by 1.0 (77%) for patients in group 2 and by 1.1 (73.3%) for patients in group 1. There were also positive changes in the dynamics of the inflammatory index before and after treatment, reducing the rate by 1.1 (78.6%) in group 2, and by 1.0 (74.1%) - in patients in group 2.

In addition, the positive trend in other studied parameters was found, including physical health. Decreased pain intensity by VPS (Fig. 2) was recorder. Reducing the severity of joint pain in most patients was observed from the first day of treatment and continued throughout the period of treatment. On average, this figure dropped by 34 (59%) in group 2 and by 21.55 (42.6%) - in group 1.

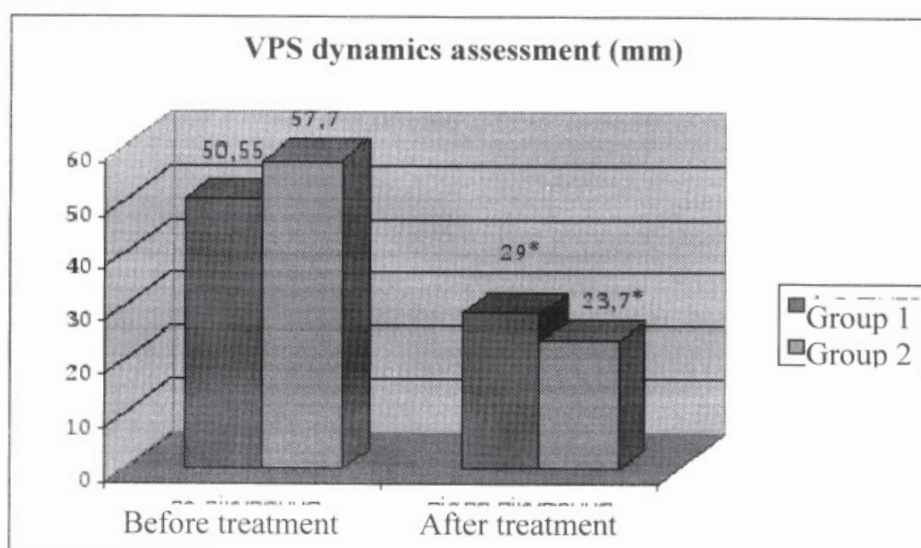


Fig. 2. VAS dynamics assessment (mm)

In general, when using NSAIDs in rheumatology, particularly when replacing one drug with another, it should be taken into account that development of anti-inflammatory effect lags in time from analgesic one. The latter can be seen in the first hours, while the anti-inflammatory one – in 10-14 days of regular intake.

There was a steady increase of flexion of the knee (Table 5) in both groups. In group 1 the range of bending in the right joint increased by 3.1%, in the left knee joint - by 2.8%. In group 2 at the beginning the range of flexion was less than in group 1, but there also was a positive trend, increasing the rate by 1.4% in the right knee joint, and by 0.4% - in the left knee joint.

Table 5

Flexion range dynamics (average), °

Knee joint	1st group		2nd group	
	Before treatment	After treatment	Before treatment	After treatment
Right	123,3±1,77	127,15±1,07*	115,2±4,1	116,8±6,8
Left	121,5±2,08	124,95±1,53	117,8±5,0	118,3±6,4

None of the patients in the study had adverse changes in general condition. There were no abnormalities in blood pressure and heart rate.

In the analysis of laboratory blood parameters (erythrocytes, hemoglobin, white blood cells and platelets) there were no significant difference before and after treatment in patients of the 1st and the 2nd groups, but in both groups there was a positive dynamics of ESR, CRP, indicating decrease of inflammation in joints (Fig. 3), which before treatment were moderately increased: CRP values in group 1 (10,25 ± 0,87) were higher almost 2 times compared to the 2nd group, which CRP level was 4,6 ± 0,8; though ESR level was higher in group 2 (25,4 ± 6,1) compared to the 1st group, where ESR was 16,9 ± 2,03.

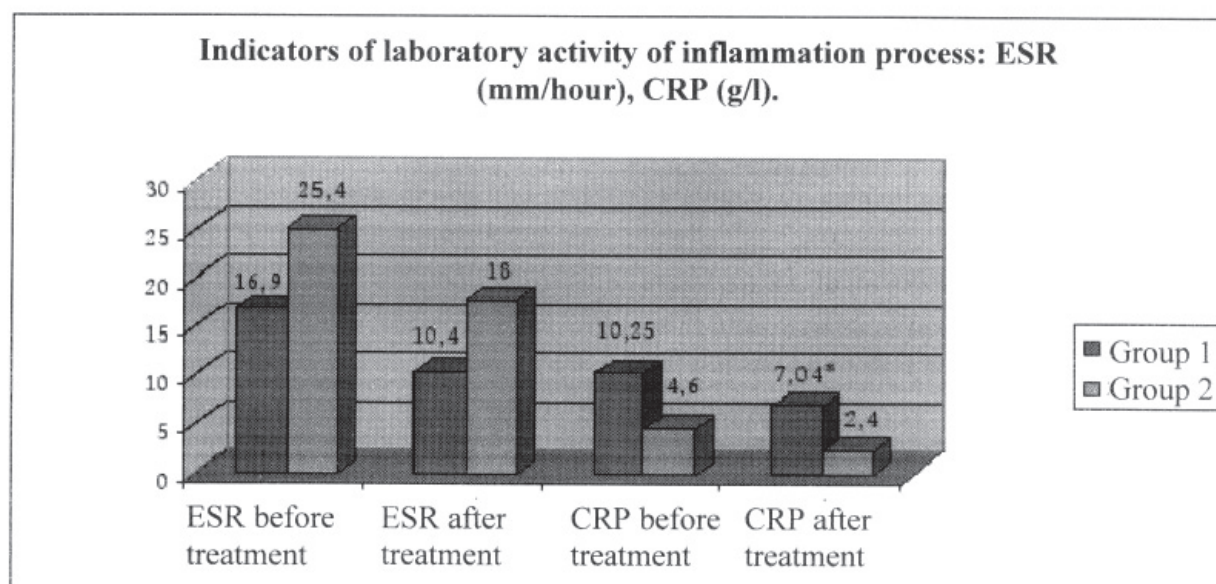


Fig.3. Indicators of laboratory activity of inflammation process: ESR (mm/hour), CRP (g/l).

In both study groups there was a positive trend for reducing laboratory indicators of inflammation activity. Thus, in general, ESR decreased by 6.5 (38.5%) and CRP level - by 3.21 (31.3%) in group 1; in group 2 ESR decreased by 7.4 (29, 1%) and level of CRP – by 2.2 (52.1%).

Separately for group 1, TNF- α , IL-6 were defined (Fig.4).

There was a decline in the dynamics of TNF- α by 3.13 (30.6%) and IL-6 – by 3.06 (25.7%) from baseline. Improving performance of CRP, TNF- α , IL-6, ESR confirms the crucial role of inflammation in the progression of OA in patients with synovitis.

Thus, in dynamics of treatment, there were changes of the studied parameters in the direction of normalization that directly pointed at reducing of inflammation. This was the case both for CRP content and for ESR content, which at the end of treatment almost normalized, confirming the effectiveness of the treatment in both groups of patients.

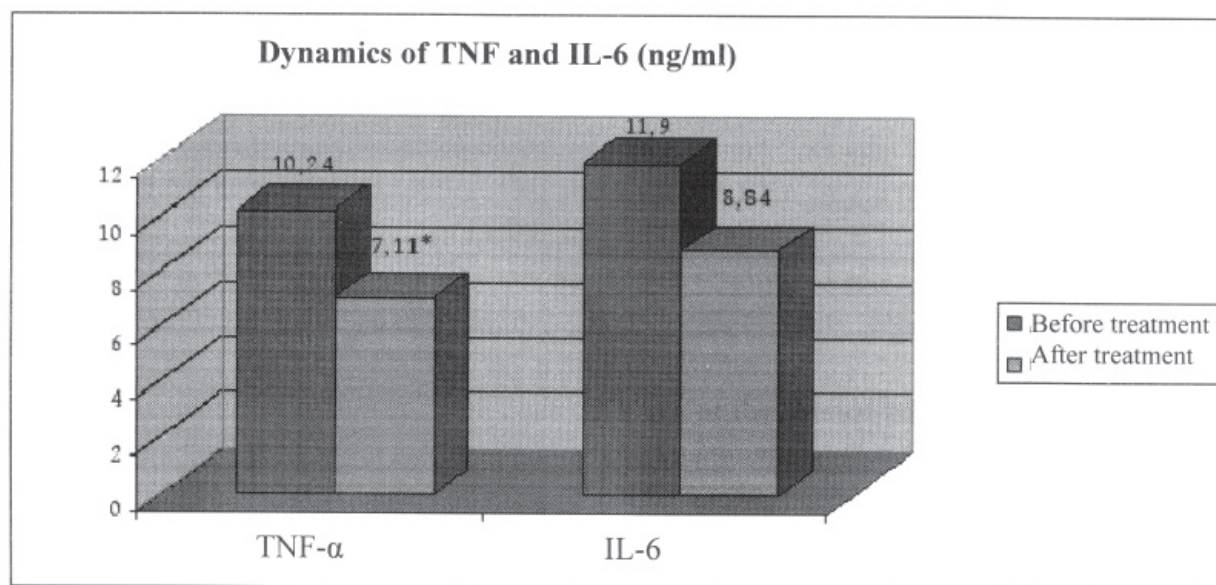


Fig. 4. Dynamics of TNF- α (ng/ml) and IL-6 (ng/ml) in patients of group 1

Assessment of lipid metabolism was performed using a lipid profile before and after treatment (Table 6).

Table 6

Indicators of a lipid profile , mmol/L

Average indicator	Before treatment	After treatment
Total cholesterol	6,26±0,25	5,24±0,12
LDL cholesterol	3,82±0,27	3,05±0,13
VLDL cholesterol	1,08±0,1	0,87±0,06
HDL cholesterol	1,2±0,05	1,37±0,04
TG	2,76±0,25	1,85±0,09*
Atherogenic index	4,42±0,34	2,85±0,14

So overall total cholesterol decreased by 1.02 (16.3%), LDL - by 0.77 (20.2%), VLDL - by 0.21 (19.4%), HDL increased by 0,17 (12.4%), TG values decreased from $2,76 \pm 0,25$ at the beginning of treatment to $1,85 \pm 0,09$ ($p < 0.05$) after 1 month of treatment, and generally decreased by 0.91 (33 %); in the overall atherogenic index decreased by 1.57 (35.5%). In general there is a clear trend towards normalization of not only HDL and triglycerides, but also all parameters of a lipid profile. Chance of a full normalization of lipid metabolism achieved a longer treatment.

Evaluation of treatment effectiveness according to the patient data are given in Table.7. In particular, there was improvement in 8 (40%) patients of group 1 and 6 (20%) – of group 2, there was a significant improvement in 12 (60%) of group 1 and in 22 (76%) of group 2, unchanged - in 2 (4%) patients in group 2, indicating the effective use of NSAIDs and fibrates combination in the treatment of patients with knee OA with synovitis and dyslipidemia.

Thus, improvement of varying degree was achieved in most patients, including positive effects on major symptoms of OA such as pain, limitation of motion, reducing the effects of synovitis, according to USI data.

Table 7

Evaluating the treatment effectiveness

Indicator, score	1st group,%	2nd group,%
Significant improvements - 2	60	76
Improvement - 1	40	20
No change - 0	0	4
Deterioration - (-1)	0	0

In group 1 there was better tolerability of treatment: in 70% - good, in 30% of patients - satisfactory. 56.6% of patients in group 2 indicated tolerability as good, 36.7% - as satisfactory, and 6.7% - as unsatisfactory (2 patients had complaints of dyspepsia after 2 weeks of receiving, that disappeared when adding to the treatment of proton pump inhibitors (omeprazole of 20 mg 2 times a day). Assessment of tolerability is given in Table.8.

Table 8

Assessment of tolerability

Indicator, score	1st group,%	2nd group,%
Good - 2	70	56.6
Satisfactory - 1	30	36.7
Unsatisfactory - 0	0	6.7

Most patients noted improvement in the general condition, the average tolerability was noted as good.

SUMMARY

1. The results showed a positive effect of the complex therapy on arthrological status, active inflammation, lipid metabolism in patients with OA with synovitis and dyslipidemia.

2. In patients of group 1, there was significant (33%) reduction in TG, the tendency to normalization of not only HDL-C and TG, but also all lipid profile indicators: the level of total cholesterol decreased by 1.02 (16.3%), LDL cholesterol - by 0.77 (20.2%), VLDL cholesterol - by 0.21 (19.4%), HDL cholesterol increased by 0.17 (12.4%), in general atherogenic index decreased by 1.57 (35.5%).

3. There was a positive trend with respect to laboratory parameters of inflammatory activity: in 100% of patients, normalization of ESR, CRP values was achieved, generally ESR decreased by 38.5%, CRP - by 31.3%; also dynamics of decline in TNF- α by 30.6% and IL-6 - by 25.7% was present, confirming the role of inflammation in the progression of OA in patients with synovitis.

4. Anti-inflammatory effect of complex therapy is confirmed by joints USI: reduction or absence of synovitis (effusion volume decreased in average by 35%).

5. Fenofibrate medicine at a dose of 250 mg daily 1 time per day demonstrated high safety and tolerability and no adverse reactions in patients with OA with synovitis and dyslipidemia.

LITERATURE:

1. Alekseenko E.Y., Govorin A.V. (2011) Changing lipid and cytokines indicators in blood of patients with primary osteoarthritis on the background of treatment with Arthra medicine. *Scientific and Practical Rheumatology*, 3: 37-40.

2. Anikin S.G., Alekseeva L.I. (2012) Chondroitin sulfate: mechanisms of action, efficiency and safety at therapy for osteoarthritis. *Modern Rheumatology*, 3: 1-5.

3. Artemenko N.A., Chvamanyya M.O. (2009) Clinical and laboratory features of different forms of osteoarthritis. *Clinical Medicine*, 2: 45-50.

4. Clinical Recommendations (2010) *Rheumatology*. Editor: Y.L. Nasonov. GOETAR-Media, Moscow, p. 326.

5. Kovalenko V.M., Bortkevich O.P. (2010) Osteoarthritis. Practical instruction. 3rd ed., ext., as amended. MORION, Kyiv, p.6-22, 72-131, 351.

6. Kopylova D.A., Ostapenko V.A. (2011) Clinical and pathogenetic features of osteoarthritis associated with obesity. *Scientific and Practical Rheumatology*, 3: 28-31.

7. Mitchenko E.I., Romanov V.Y., Belyaeva T.V., Chulaevskaya I.V. (2009) Fenofibrate therapy effect on lipid spectrum of plasma and insulin resistance of patients with metabolic syndrome and diabetes of the 2nd type. *Heart and vessels*, 3: 77-82.

8. Mironov S.P., Yeskin N.A., Orletsky A.K. et al (2006) Sonography of a knee joint pathology. *SonoAce-Ultrasound*, 14: 78-89.

9. Naumov A.V., Shamuilova M.M. (2012) Osteoarthritis – Decisions Strategy: From the point of view of contemporary knowledge. *Consilium Medicum*, 2: 3-6.

10. Popkova T.V., Novikova D.S., Nasonov E.L. (2011) Interleukin-6 and cardio-vessel pathology in rheumatoid arthritis. Scientific. Scientific and Practical Rheumatology, 4: 64-72.
11. Smiyan S.I., Gusak S.R. (2008) Evaluating the effectiveness of treating osteoarthritis in patients with overweight and metabolic syndrome. Scientific and Practical Rheumatology, 4 (10): 49-53.
12. Sattar N., Crompton P., Cherry L. (2007) Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study. Arthr. Rheum., 56: 831-839.

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Address for correspondence:

Ivanova Kateryna Anatoliivna


E-mail: ivanovakatya09@rambler.ru

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Адреса: 01601 Україна, Київ, Печерський узвіз, 3, офіс 204.

Контактний номер телефону: (+38 044) 229 6239

Перекладач  Михайленко Ганна Володимирівна

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Address: Office 204, 3 Pecherskyi uzviz, Kyiv, 01601 Ukraine.

Phone No. (+38 044) 229 6239

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