ORIGINAL INVESTIGATIONS

Olokizumab in patients with inflammatory phenotype of osteoarthritis, treatment experience

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Objective: *to investigate the efficacy and safety of olokizumab (OKZ) in patients with knee osteoarthritis (OA) with synovitis, persistent pain and ineffectiveness of previous conservative therapy.*

Material and methods. *The study included 15 patients with stage II–III knee OA who fulfilled the ACR criteria and had pain ≥50 mm on a visual analogue scale (VAS), synovitis and treatment failure. The age of patients ranged from 54 to 75 years; the duration of the disease was from 1 to 23 years. The duration of the study was 12 weeks, during which the patients received 3 subcutaneous injections of OKZ at a dose of 64 mg. The effectiveness of the treatment was assessed by the dynamics of pain intensity according to VAS, WOMAC and KOOS indices, the values of the DN4 questionnaire and the quality of life according to EQ-5D. In addition, the general assessment of the patient's health (GHA) according to VAS, the assessment of treatment efficacy by doctor and patient and the need for non-steroidal anti-inflammatory drugs (NSAIDs) were considered. All patients underwent laboratory testing.*

Results and discussion. *During treatment, there was a significant decrease in pain intensity according to VAS, a statistically significant improvement in the KOOS and WOMAC indices ($p<0.05$), quality of life according to the EQ-5D questionnaire and GHA. Patients and doctors rated the treatment results very positively: an improvement or significant improvement was observed in 92.3% of cases. Adverse events were identified in 4 patients, which in 2 cases served as the reason for discontinuation of OKZ treatment and termination of participation in the study. During treatment with OKZ, a statistically significant decrease in CRP and ESR values, an increase in the concentration of interleukin 6 ($p=0.003$), COMP ($p=0.03$) and PIINP ($p=0.01$) were observed.*

Conclusion. *The results obtained suggest a significant symptomatic and anti-inflammatory effect of OKZ in patients with the inflammatory phenotype of OA.*

Keywords: *osteoarthritis; inflammatory phenotype; interleukin 6; olokizumab.*

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Osteoarthritis (OA) is one of the most prevalent diseases of joints, and its incidence keeps increasing. According to the global study investigating burden of diseases as of 2020, 7.6% of the global population live with diagnosed OA, which is equivalent to 595 mln (95% confidence interval [CI] 535–656). Between 1990 and 2020, the number of patients with OA increased by 132.2% (95% CI 130.3–134.1) and by 2050, as compared to 2020, the number of patients with OA of knee joints is expected to increase by 74.9% (95% CI 59.4–89.9), wrist joints – by 48.6% (95% CI 35.9–67.1), hip joints – 78.6% (95% CI 57.7–105.3), other locations – by 95.1% (95% CI 68.1–135) [1].

According to present-day understanding, OA is considered to be a heterogeneous disease, presenting with distinct phenotypes and endotypes [2]. Differentiation between OA phenotypes / molecular endotypes is among strategic priorities of research activities focused in this area, as in future this would enable individually tailored treatment and more reasonable use of healthcare resources.

Currently many researchers acknowledge inflammatory OA phenotype and endotype. Most of its pathophysiological mediators have been identified and treatment approaches are being developed. Synovitis, a manifestation of inflammation, play a key role within such phenotype/endotype. This phenotype is believed to be characterized by severe pain, impaired joint function a rapid disease progression [6,7].

Instrumental examinations, including magnetic resonance imaging (MRI) and ultrasound examination, complemented by measurements of biochemical markers, play an important role in the diagnosis of inflammatory OA. E.g. Dell'Isola et al. [8] proposed using MRI evidence of synovitis of maximum severity – the score of 3 (severe effusion/synovitis) according to MRI Osteoarthritis Knee Score (MOAKS) – to identify such patients. Y. Henrotin [9] notes that the following biomarkers must be considered as relevant for this phenotype: oncostatin M, a cytokine belonging to the interleukin (IL) 6 family, and a CRP metabolite. Identification of elevated serum CRP, C1M and C3M (fragments of mature collagen types I and III degradation mediated by matrix metalloproteinases, MMP) may be promising for the diagnosis of such endotype variant [10].

The recognition of the crucial role of inflammation in the pathogenesis of this phenotype/endotype provided rationale for investigating efficacy of medications affecting pro-inflammatory

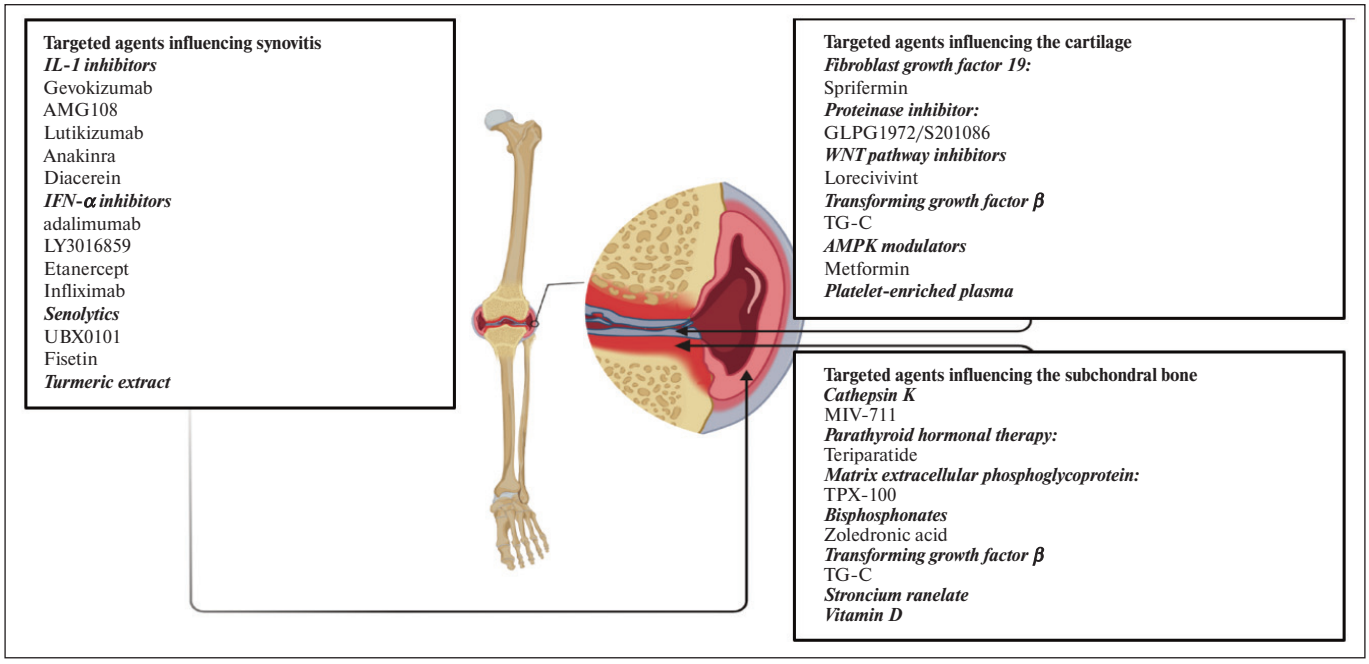

Fig. 1. *Potential disease-modifying drugs for OA (adapted from [11])*

cytokines (see Figure 1), mainly tumor necrosis factor alpha (TNF-α), IL1 and IL-6 [11]. Currently there is lack of compelling evidence regarding the use of biologic agents in OA, as medicines belonging to this class (tocilizumab, adalimumab, etanercept, gevokizumab, lutikizumab, anakinra, canakinumab etc.) are either investigated in different phases of their clinical development programs or have demonstrated lack of efficacy [11, 12].

Among potential disease-modifying medications to treat this OA phenotype olokizumab (OKZ) is of particular interest; this Russian product is a humanized monoclonal antibody IgG4-κ blocking signal pathways at the stage of final assembly of the hexameric complex containing IL-6, IL-6 receptor (IL-6R) and gp130 [13]. This IL, among other cytokines belonging to the IL-6 family of proteins, plays one of the key roles in the inflammatory response in OA, and it is the main target for therapeutic interventions, which provides rationale for investigating OKZ efficacy and safety in patients with inflammatory phenotype of this disease [14]. Neither in the Russian Federation nor in other countries this medication has been investigated in any trials in OA.

Objective of the study was to evaluate efficacy and safety of OKZ administration in patients with knee OA and synovitis, persistent pain and failure of prior medical treatment.

Materials and methods

Inclusion criteria: men and postmenopausal women aged 45-75; the diagnosis of primary tibiofemoral OA meeting ACR (American College of Rheumatology) criteria, Kellgren-Lawrence stages II-III, pain during walking as ≥50 mm according to the Visual Analogue Scale (VAS); presence of recurrent/persistent knee synovitis; the need for non-steroidal anti-inflammatory drugs (NSAIDs), administered for at least 30 days in the previous 3 months; failure of prior medical treatment for OA, including various Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA); negative TB skin test, no radiological findings in chest X-ray / fluorography within the last 6 months; signed Informed Consent Form.

Exclusion criteria: Kellgren-Lawrence OA radiological stage I or IV; secondary knee OA; hereditary fructose intolerance (as the medicine contains sorbitol), intraarticular injections of steroids, hyaluronic acid derivatives, platelet-rich plasma (PRP) treatment within 3 months prior to the study; hypersensitivity to the medicine or its excipients; other rheumatic diseases; chondrocalcinosis; osteonecrosis of the femoral head and/or femoral/tibial condyles, surgery on evaluated joint; gastric or duodenal ulcer within the previous 12 months; severe liver, renal, blood, lung and cardiovascular comorbidities as well as other diseases that, in the Investigator's opinion, could influence outcomes; type 1 diabetes mellitus, decompensated type 2 diabetes mellitus; history of gastrointestinal bleedings or cerebrovascular bleedings; history of diverticulitis or high risk perform gastrointestinal perforations; impaired hematopoiesis: hemoglobin <120 g/L in women and <140 g/L in men, WBC <3,500/mm^3, platelet count <100,000/mm^3; impaired renal function (creatinine clearance <90 mL/min); aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ≥ upper limit of normal; history of any malignancy, except non-melanoma skin cancer or localized cervical carcinoma in situ successfully treated; use of live vaccines within the previous 6 months; intolerance/contraindications to NSAIDs; extended (including even one episode) herpes simplex infection, recurrent or extended (including even one episode) herpes zoster infection; HIV, history of active viral hepatitis (B, C) or liver cirrhosis; acute and chronic infectious diseases; patients' inability to comply with the protocol requirements; women with preserved menstrual function; alcohol abuse, including history of; simultaneous participation in a clinical trial of another medication.

Ethical review. Before the study initiation (October 05, 2021, minutes #19) approval from Research Board of the Federal State Budgetary Research Institution "V.A. Nasonova Rheumatology Research Institute" was received for the study. The study conduct was approved by the local Ethics Committee of "V.A. Nasonova Rheumatology Research Institute" on October 28, 2021 (minutes #10, state assignment #1021051403074-2).

Table 1. Characteristics of patients (n=15)

Parameter	Value
Age, years, median [25th; 75th percentiles]	64 [58; 68]
OA duration, years, median [25th; 75th percentiles]	8 [5; 15]
BMI, kg/m^2, median [25th; 75th percentiles]	31 [27; 36]
OA stage, %: II III	 53,3 46,7
VAS pain assessment, mm, median [25th; 75th percentiles]	65 [55; 75]
Synovitis, %: Clinical According to ultrasound examination	 100 100
DN4 ≥4, %	33,3

Fifteen patients (80% women and 20% men) were enrolled into the study. The patients' age was 54 to 75 years, disease duration ranged from 1 to 23 years. Patients' clinical characteristics are presented in Table 1. Comorbidities included: arterial hypertension in 73%, obesity in 66.7%, dyslipidemia in 13%, type 2 diabetes mellitus in 20%, coronary artery disease in 13%, urolithiasis in 13, osteoporosis in 6%, chronic gastritis in 6%, primary hypothyroidism associated with autoimmune thyroiditis in 6%. All patients had to rely on NSAIDs for pain, mostly aceclofenac (26.7%), nimesulide (26.7%) and ibuprofen (20%).

The study duration was 12 weeks, during which patients received 3 subcutaneous injections of OKZ 64 mg (the first administration -on the premises of V.A. Nasonova Rheumatology Research Institute and 2 subsequent - on an out-patient basis): visit (V)1 – treatment initiation (1st drug administration); V2 – 1 month after treatment initiation (2nd drug administration); V3 – 2 months after treatment initiation (3rd drug administration); V4 – 3 months after treatment initiation (4th drug administration)

Treatment efficacy was evaluated based on knee joint walking pain intensity as measured by VAS, WOMAC (Western Ontario

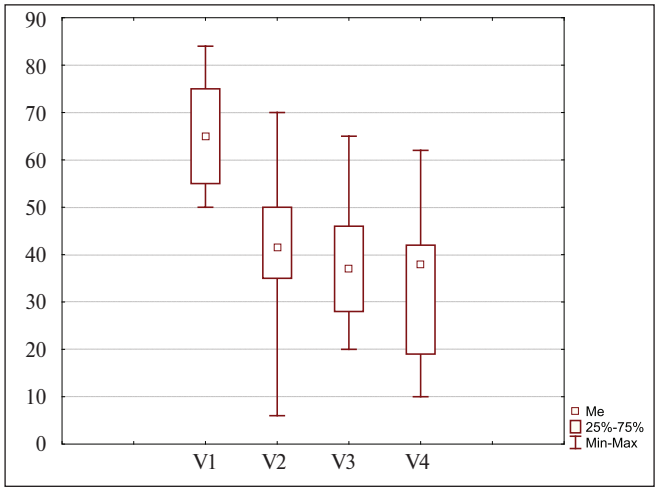

Fig. 2. *Dynamics of knee pain intensity according to VAS, mm*

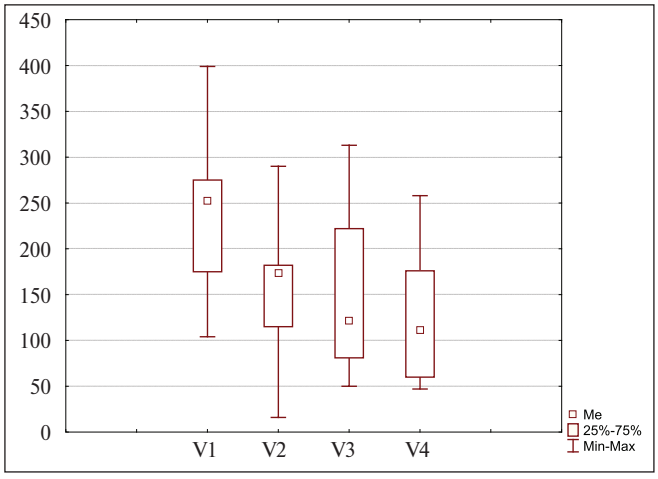

Fig. 3. *Pain dynamics according to WOMAC, mm*

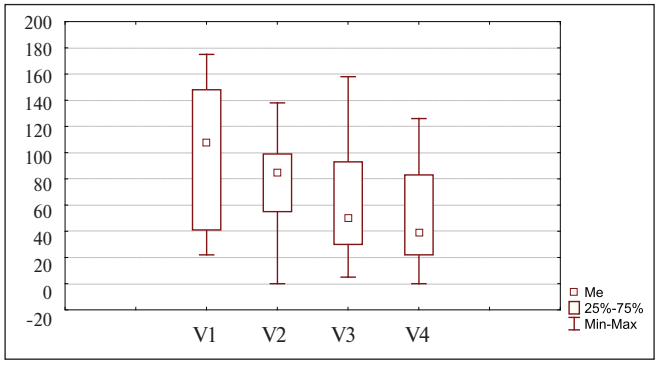

Fig. 4. *Stiffness dynamics according to WOMAC, mm*

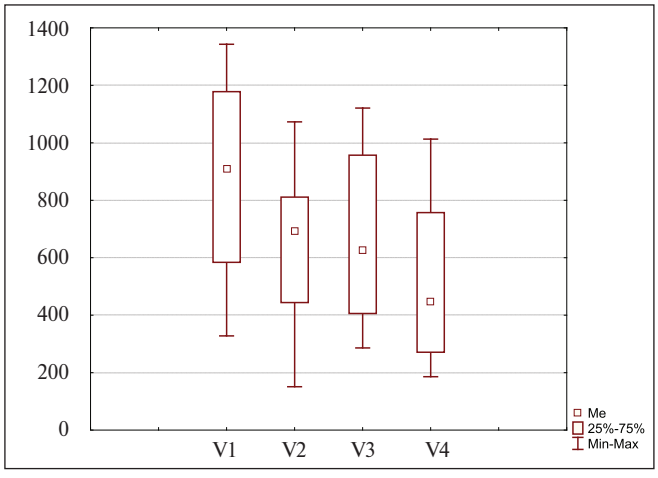

Fig. 5. *Functional insufficiency dynamics according to WOMAC, mm*

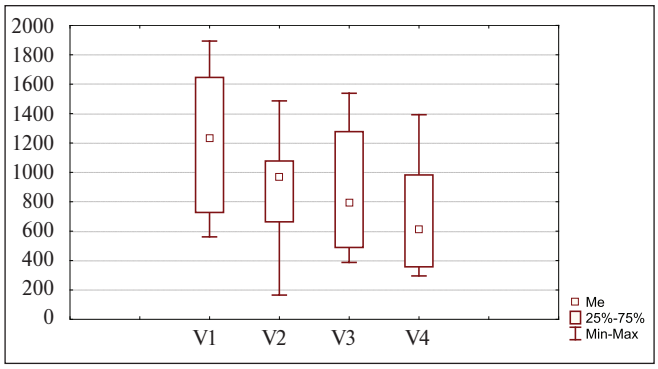

Fig. 6. *Dynamics of the total WOMAC index, mm*

and McMaster Universities Osteoarthritis Index) and KOOS (Knee Injury & Osteoarthritis Outcome Score – the score assessing knee joint function and patient's function in daily living, Function in Sport and Recreation); DN4 questionnaires (Douleur Neuropathique 4 Questions) and quality of life EQ-5D (EuroQol-5 Dimensions) scores. Additionally, patient's assessment (PtGA) of health status was measured by VAS, treatment efficacy was measured by both the doctor and the patient ("significant improvement", "improvement", "cannot determine", "no change", or "worsening"), and the need in NSAIDs was determined. All patients on Visits 1-4 underwent blood tests, with the following parameters evaluated: erythrocyte sedimentation rate, total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), ALT, AST, creatinine and C-reactive protein. Knee joint ultrasound examination was performed to all patients at baseline and at the end of the study. The following immunological parameters were assessed by enzyme linked immunosorbent assay: IL-6 level (the upper limit of normal based on measurements in 15 serum samples from healthy donors – 0.005 ng/mL); MMP3 (the enzyme responsible for degradation of cartilage proteoglycans, upper limit of normal in women – 20 ng/mL, in men – 40 ng/mL); Human Cartilage Oligomeric Protein, COMP – a marker of cartilage tissue degradation, the upper limit of normal based on measurements in 15 serum samples from healthy donors – 10.6 ng/mL); procollagen type II N-terminal propeptide (PIINP, a new biomarker reflecting cartilage formation, the upper limit of normal based on measurements in 15 serum samples from healthy donors – 8115 ng/mL); C-telopeptide of type I collagen, CTX-I, a marker of bone remodeling, the upper limit of normal based on measurements in 15 sera from healthy donors – 0.611 ng/mL).

The frequency and nature of adverse events (AEs), including clinically significant laboratory abnormalities during the observation period, and their relationship to the investigational product, were evaluated as safety parameters.

Statistical analysis was done using Statistica 12.0 software (StatSoft Inc., USA). Analysis for normality of distribution was performed using the Kolmogorov–Smirnov and Shapiro–Wilk tests, as well as frequency analysis. Methods of descriptive statistics were applied calculating minimal, maximal and mean values, standard deviations, median and interquartile range (median [25th; 75th percentiles]), as well as Wilcoxon criterion and χ^2. Friedman repeated measure analysis of variance was performed to compare parameter values over time. Differences were considered statistically significant at $p<0.05$.

Results. Statistical analysis was performed both in the intention-to-treat (ITT) population and in the per protocol (PP) population. The ITT population included 15 patients, while the PP population included 13 patients. Two patients discontinued from the study due to AE development: one after V1, the other one after V2. Results for the ITT and PP populations did not differ; therefore, data from the ITT population analysis are provided hereunder.

Results for the main efficacy parameters demonstrated significant improvements. Specifically, a statistically significant improvement in walking pain as measured by VAS was observed (see Figure 2) as early as by V2 (median reduced from 65 [55; 75] to 41.5 [35; 50] mm; p=0,001), further reduction of this parameter continued throughout the observation period (by B3 - to 37 [28; 46] mm, and by V4 - to 38 [19; 42] mm; p=0,001). Good treatment response (pain improvement by ≥50% from baseline) was achieved in 53.8% patients; VAS pain improvement to <40 mm – in 69.2%.

The same pattern was observed for pain, stiffness, functional limitations according to WOMAC and the total WOMAC score (see Figures 3-6). Statistically significant improvement of those parameters was observed by V2 (in 1 month). Subsequent reduction of all components and the total WOMAC score was observed throughout the treatment period, demonstrating a good therapeutic effect regarding symptoms. E.g. median pain WOMAC score at the treatment initiation (at V1) was 252 [175; 275] mm, at V2 – 174 [115; 182] mm, at V3 – 122 [81; 222] mm, at V4 (at the end of treatment) - 111 [60; 176] mm; stiffness – 108 [41; 148], 84.5 [55; 99], 50 [30; 93] and 39 [22; 83] mm; functional limitations – 910 [584; 1178], 694 [444; 811], 626 [406,5; 957] and 447 [271,5; 757] mm; total WOMAC score – 1237 [729; 1648], 969,5 [665; 1079], 798 [491; 1279] and 612 [359; 984] mm respectively (p<0,05).

Changes in KOOS scores of pain, symptoms, function in daily living and quality of life were statistically significant (see Table 2). Treatment efficacy was also supported by quality of life improvement as measured by the EQ-5D tool (see Figure 7): at baseline mean and median were 0.29 and 0.52 [-0.02; 0,52], while at the end of treatment – 0.6 and 0.52 [0.52; 0,68] respectively (p=0.01). Similar results were observed with patient's global assessment (PtGA) as measured by VAS (see Figure 8). During the first month it improved and its median increased from 55 [40; 60] to 61 [53; 70] mm (p=0,002). The achieved effect was sustained during subsequent observation (V3 – 65 [58; 75] mm and V4 – 70 [60; 75] mm; p=0,001 from V1).

The DN4 questionnaire results demonstrated a trend to a reducing number of patients with neuropathic pain and/or central sensitization (DN>4): 38.5 and 20% at baseline and at the end of treatment respectively (p>0.05).

Results confirm significant treatment efficacy against symptoms: median time from treatment initiation to analgesic effect was 33 [14; 45] days.

Patient improvement on OKZ treatment is also demonstrated by the reduced need in NSAIDs. At baseline, 100% patients took various NSAIDs for pain, whereas in 12 weeks 66.7% of them switched to reduced doses or to the pro re nata (PRN) administration. Similar changes were demonstrated by treatment response assessments – in doctors' and patients' opinions (see Figures 9 and 10): by the end of treatment most patients noted improvement or significant improvement (76.9 and 15.4% respectively), lack of response in 7.7% cases, no cases of worsening.

The data based on ultrasound parameters were noteworthy. A trend towards reducing synovial membrane thickness was demon-

Table 2. Evaluation of treatment efficacy according to KOOS, Me [25th; 75th percentile]

Parameter	V1 (n=15)	V2 (n=14)	V3 (n=13)	V4 (n=13)	P*
Pain	44,4 [33,3; 55,6]	54,2 [50; 61,1]	55,6 [47,2; 66,7]	63,9 [50; 66,7]	<0,01
Symptoms	50 [35,7; 57,1]	57,1 [46,4; 71,4]	64,3 [50; 75]	64,3 [53,6; 67,9]	<0,05
Daily activity	47,1 [35,3; 50]	50,8 [47,1; 63,2]	57,4 [48,5; 63,2]	57,8 [51,5; 70,6]	<0,003
Quality of life	25 [12,5; 43,8]	31,3 [18,8; 63,2]	31,3 [31,3; 63,2]	43,8 [31,3; 70,6]	<0,05

* Significance of differences between V1 and V2, V3, V4.

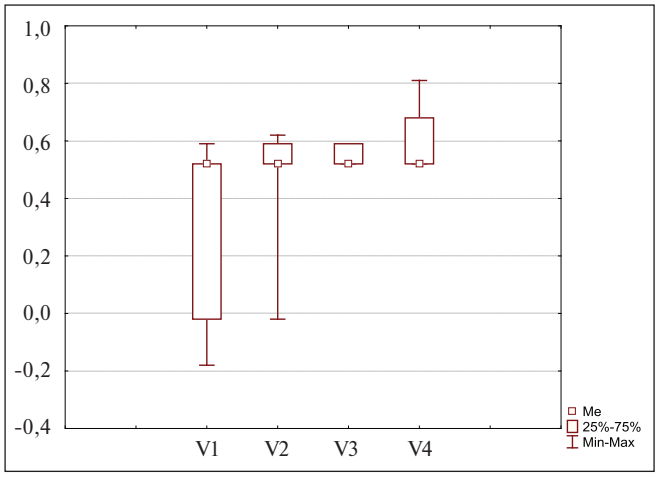

Fig. 7. *Dynamics of EQ-5D*

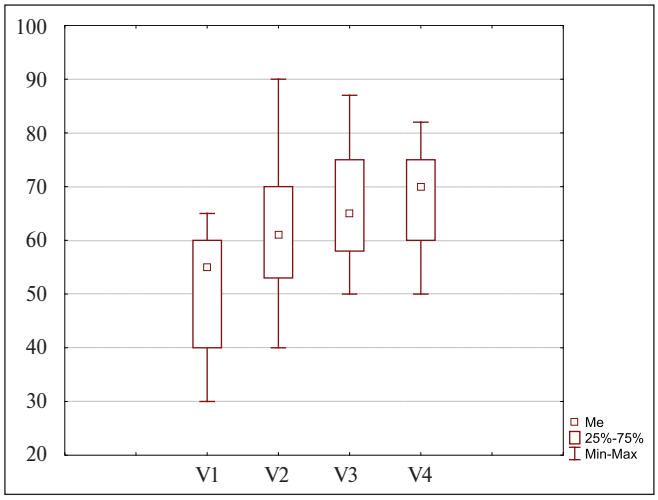

Fig. 8. *Dynamics of GHA according to VAS, mm*

strated: at baseline its thickness was 3.7 [3.2; 4.5] mm, by V4 – 3.5 [3.1; 3.6] mm (p=0.07). The number of subjects with tenosynovitis of lateral collateral ligaments and Baker's cyst decreased – 75 vs 41.7% (p=0.21) and 66.7 vs 33.3% (p=0,22) respectively.

Treatment was accompanied by a significant reduction in CRP (see Figure 11) and ESR (see Figure 12), supporting the anti-inflammatory action of the medication: V1 – 2.9 [1; 4] mg/L and 13 [4; 22] mm/h, V2 – 0,3 [0,2; 1,7] mg/L and 5 [2;6] mm/h, V3–0.4 [0.2; 0.8] mg/L and 3.5 [2; 6] mm/h, V4 – 0.35 [0.2; 0.95] mg/L and 2 [2; 4] mm/h respectively (p<0.005 at all visits compared to V1).

Among immunological parameters, a higher concentration of COMP, which is a marker of cartilage tissue degradation, and IL-6, which is a pro-inflammatory cytokine, in OA patients compared to controls (15 age- and BMI-matched subjects without OA), reiterating the role of inflammation in the pathogenesis of this disease (see Table 3).

In 3 months, accompanying significant and rapid improvement of main OA symptoms on OKZ treatment (3 subcutaneous administrations) statistically significant elevation of IL-6 (p=0.003), COMP (p=0.03) and PIINP (p=0.01) were observed. Before OKZ treatment initiation IL-6 levels had a statistically significant inverse correlation to PtGA (r=-0.75; p=0.007), whereas IL-6 elevation was associated with obesity (r=0.62, p=0.03). COMP concentration at V1 demonstrated inverse correlation with EQ-5D at V1 (r=-0.83; p=0.002). Other immunological parameters did not correlate to clinical or laboratory values – neither at baseline nor by the end of the observation period (p>0,05). Inverse correlation between MMP3 and PIINP was found (r=-0,83; p<0,001).

After 1 and 2 months of treatment platelet reduction was observed compared to baseline, whereas hemoglobin, RBC and WBC levels did not demonstrate significant changes (see Table 4). Insignificant elevation of ALT levels by Visit 2 and 3 (see Figure 13) and LDL levels by Visit 3 (see Figure 14) was observed, compared to V1 levels (p<0.05), but in 3 months any such changes abrogated. No statistically significant OKZ effect was found on creatinine, AST, total cholesterol, triglycerides or HDL levels.

During 3 months of observation 4 AEs were reported in 4 patients: two of them caused OKZ discontinuation and withdrawal from the study. One case involved a serious AE of bilateral pneumonia of unknown etiology, requiring in-patient hospitalization, 10 days after the first subcutaneous administration of OKZ. This AE, probably related to the investigational product, resolved with antibacterial treatment, the use of steroids and mucolytic agents. The second case involved allergic dermatitis 2 days after the 2nd OKZ administration on the dorsal surface of wrists, upper chest and back. The event was successfully managed at the place of the patient's residence by a dermatologist (antihistamines, intramuscular steroids). Causal relationship between this AE and OKZ administration was classified as possible, it is also noteworthy that the day before the onset of dermatitis the patient had started administration of three herbal supplements. Other 2 cases involved insignificant ALT elevation not requiring any additional treatment.

Discussion. Overwhelming complexity and heterogenicity of OA pathogenesis significantly complicate treatment and cause

Table 3. Dynamics of immunological markers concentrations in the blood serum of patients with OA during treatment with OKZ, ng/ml, Me [25th; 75th percentile]

Parameter	V1 (n=12)	V4 (n=12)	Control group (n=15)	p
IL6	0,09 [0,03; 0,16]	300 [300; 300]	0,007 [0,003; 0,009]	0,003* 0,003**
MMP3	10,1 [9,1; 11,7]	13,8 [10,9; 20]	–	>0,05
COMP	1,25 [0,17; 33,3]	31,7 [0,03; 46]	0,018 [0,001; 0,73]	0,02* 0,03**
PIINP	3603 [3044; 3739]	3739 [3525; 5118]	3418,3 [3217,6; 5331,6]	>0,05* 0,01**
CTX-I	0,32 [0,19; 0,46]	0,32 [0,21; 0,38]	0,21 [0,17; 0,32]	>0,05

*Comparison of the parameter between the main study group and the control group at V1; ** Comparison of the parameter in the main study group between V1 and V4.

negative results of clinical trials; however, they also provide incentive for pursuing new therapeutic targets. E.g. present-day understanding of OA pathogenesis, recognizing the central role of inflammation, providing rationale for investigating medicines targeting inflammatory mediators. IL-6 inhibitors offer significant promise for developing new approaches to treating such disease phenotype.

IL-6 plays an important role in many immune, metabolic, cardiovascular, neuroendocrine and neuropsychological diseases, as well as in OA pathogenesis. Evidence is available confirming elevated IL-6 in the serum and synovial fluid in OA patients compared to healthy (control) subjects [15–17]. It is associated with the disease onset and progression [18–20]; it can also be considered as a marker of cartilage tissue destruction. Several studies demonstrated that IL-6 levels in the synovial fluid significantly increase when cartilage defects are present, even before macroscopically notable OA manifestations [21, 22]. In our study IL-6 concentrations in blood serum were also higher than in the control group (p=0.003).

The synovial membrane (where this cytokine is produced due to activation of synovial fibroblasts and plasma cells [23–25]) and infrapatellar fatty tissue [26] are believed to play the key role in IL-6 secretion in OA. E. Diestel et al. [27] have demonstrated that in women with OA IL-6 production in the infrapatellar fatty tissue is 2 times higher than in visceral tissues. Obesity per se is associated with a small but significant elevation of serum IL-6 levels. Adipocytes and macrophages of the fatty tissue are recognized as the main sources causing elevated blood IL-6. In addition, in obese OA patients synovial fibroblasts also begin production of IL-6 in greater amounts compared to subjects with normal body weight [28]. In this study, 66.7% patients were obese. Also, direct proportionality was established in this study between obesity and serum IL-6 (r=0.62, p=0.03). This suggests that IL-6 could also be potentially relevant target in the metabolic OA phenotype, frequently overlapping with the inflammatory phenotype.

Experimental research has confirmed that targeting IL-6 can be a promising treatment strategy for OA as it mitigates cartilage destruction, synovial inflammation and subchondral bone damage [26]. However, so far only isolated clinical trials investigating efficacy of tocilizumab, an IL-6R inhibitor, have been done.

P. Richette et al. [29] investigated tocilizumab efficacy in OA of wrist joints in a multicenter 3-month randomized double blind placebo-controlled trial. The trial enrolled 91 patients with verified diagnosis of wrist OA, with at least 3 tender joints, pain >40 mm VAS, no response to analgesics or NSAIDs. Patients received 2 intravenous infusions of tocilizumab (8 mg/kg) or placebo (at Weeks 0 and 4). No benefits of an IL-6R inhibitor compared to placebo were found. This contradicts to results obtained by J.M. Sanchez et al. [30] evaluating efficacy of such treatment in 24 patients with inflammatory phenotype – erosive OA of wrist joints.

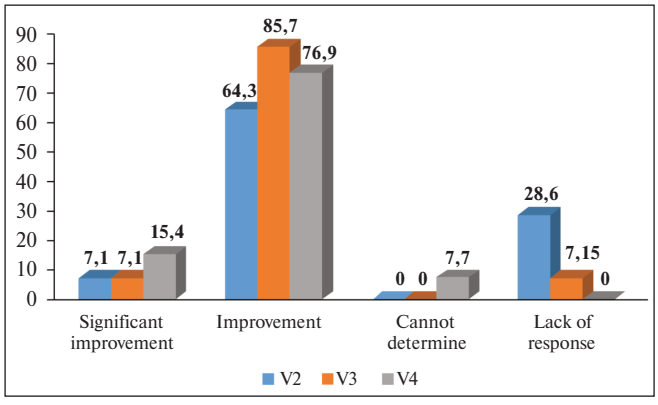

Fig. 9. *Assessment of efficacy of therapy by doctor, %*

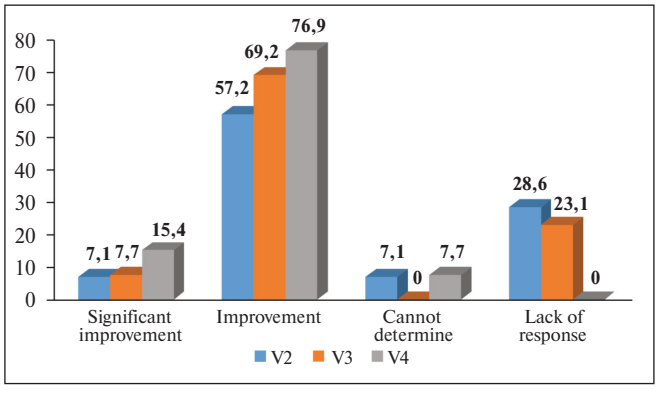

Fig. 10. *Assessment of efficacy of therapy by patient, %*

Table 4. Dynamics of laboratory parameters in patients with OA during therapy with OKZ, Me [25th; 75th percentile]

Parameter	V1	V2	V3	V4	p
Hemoglobin, g/L	139 [132; 146]	136 [130; 145]	144 [132; 151]	142 [130; 150]	>0,05
RBC, ·10⁹L	4,7 [4,3; 4,9]	4,5 [4,3; 4,9]	4,7 [4,4; 4,9]	4,6 [4,4; 4,8]	>0,05
WBC, ·10⁹L	6,0 [4,9; 6,8]	5,4 [5,1; 5,9]	5,4 [4,9; 7,2]	5,7 [5,1; 6,1]	>0,05
Platelets, ·10⁹L	227,5 [197; 246]	215 [179; 225]	212 [188; 235]	217 [174; 243]	**<0,001***,**
ALT, U/L	18,4 [12,4; 22,9]	27,2 [18,3; 29,6]	22,8 [17; 37,4]	19 [15,5; 25,1]	**<0,005***,**
AST, U/L	18,4 [15,8; 21,6]	22,9 [17,2; 28,5]	19,8 [17,5; 26,2]	19,8 [17,8; 21,7]	>0,05
Creatinine, μM	67,5 [57; 87,1]	66,6 [56,8; 74,3]	70,1 [58,6; 78,1]	73,6 [62,4; 79,6]	>0,05
Total cholesterol, mM	5,0 [4,3; 6,3]	5,5 [4,6; 6,5]	5,7 [4,5; 6,7]	4,9 [4,1; 5,8]	>0,05
LDL, mM	2,8 [1,9; 4,1]	3,1 [2,7; 4,0]	3,7 [2,6; 4,9]	2,8 [2,1; 3,5]	**<0,01****
HDL, mM	1,4 [1,2; 2,0]	1,5 [1,3; 1,9]	1,6 [1,4; 2,1]	1,5 [1,2; 2,0]	>0,05

* Significance of difference between V1 and V2; ** between V1 and V3.

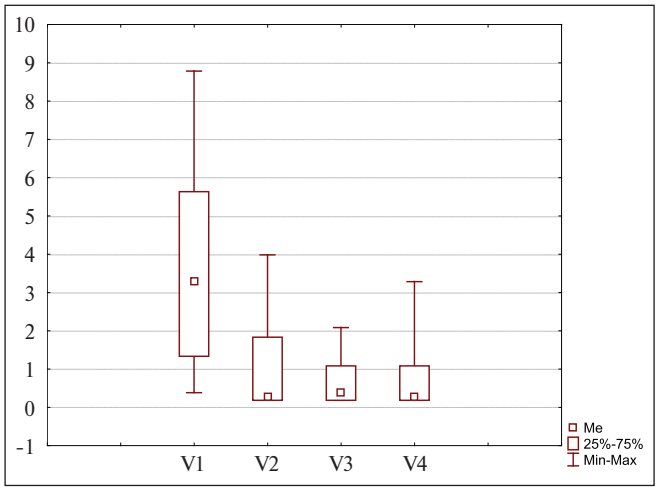

Fig. 11. *Dynamics of CRP level, mg/l*

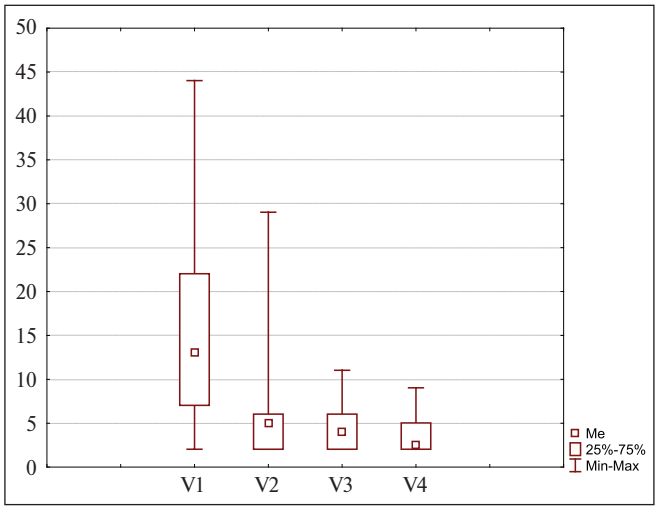

Fig. 12. *Dynamics of ESR, mm/h*

Treatment resulted in a significant improvement of the AUSCAN score – both total and its separate subscores, reduction of VAS pain, ESR, CRP and IL-6. Authors conclude that efficacy and safety of tocilizumab in patients with OA must be further investigated in randomized controlled trials.

As of now, no monoclonal antibody to IL-6, its receptors or gp130Fc (tocilizumab, vobarilizumab, satralizumab, sarilumab, siltuximab, OKZ, sirukumab, clazakizumab, MEDI 5117, olamkicept etc.) has been approved for OA treatment. This is the first study investigating efficacy and safety of OKZ, and IL-6 inhibitor, in inflammatory phenotype of knee OA. The obtained results demonstrate significant improvement of symptoms and anti-inflammatory effect. Treatment was associated with by a significant reduction of pain intensity, as assessed by VAS, improvement of KOOS and WOMAC scores. OKZ significantly increased quality of life, as assessed by EQ-5D and patient's global assessment. It is noteworthy that treatment outcomes were very favorably assessed by both patients and doctors, reporting improvement or significant improvement in 92.3% cases. Treatment was associated with a trend towards less patients having neuropathic pain and/or central sensitization, identified based on the DN4 questionnaire: by 18.5% in 3 months of observation.

An important result of the study is the confirmation of the anti-inflammatory action of the medication, as evidenced by significant CRP and ESR reduction. Improvements were also noted in knee ultrasound results: synovial thickness decreased and the number of patients having Baker's cyst reduced.

Our results describing the changes in IL-6 and other markers during OKZ treatment over time are particularly interesting. E.g. after 3 months of OKZ treatment in patients with inflammatory OA phenotype significant clinical improvement was accompanied by elevation of IL=6 (by thousands times), COMP and PIINP. The latter parameters have opposing actions: whereas COMP is a marker of collagen type II degradation, PIINP is a marker of cartilage formation. There are no literature sources elucidating such phenomenon, which may be related to improved metabolism

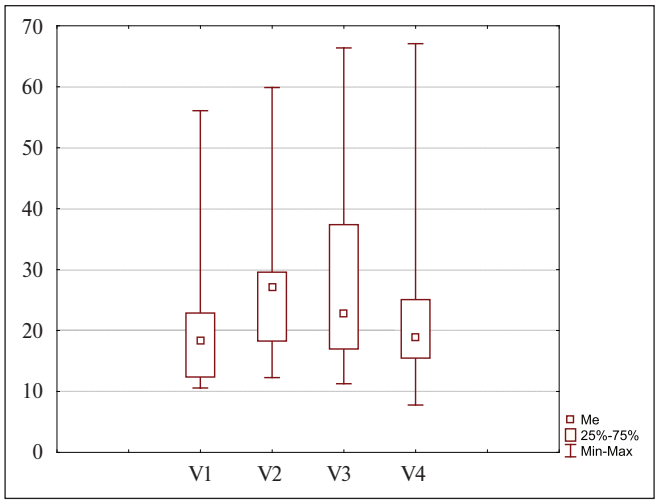

Fig. 13. *Dynamics of ALT level, units/l*

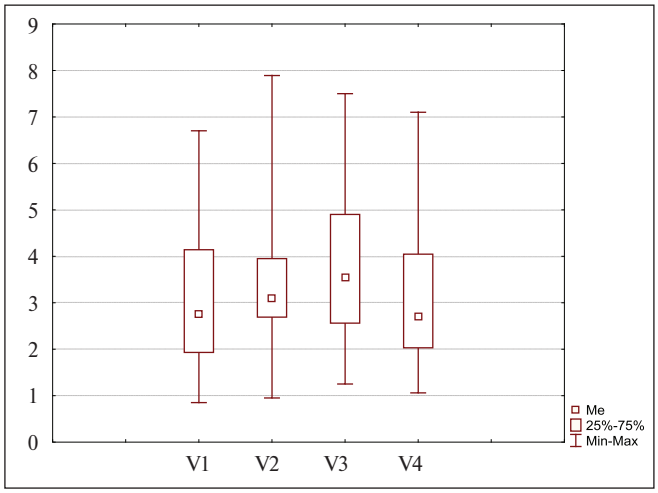

Fig. 14. *Dynamics of LDL level, mmol/l*

of the cartilage tissue by OKZ treatment but requires further investigation.

Elevation of IL-6 blood concentration during OKZ administration has been observed by other authors as well, however, there is no detailed explanation to such perplexing phenomenon. N.A. Lapkina et al. [13] after 3 months of OKZ treatment in 10 patients with rheumatoid arthritis also observed a statistically significant elevation of IL-6 ($p<0.01$) accompanied by a reduction in disease activity scores and CRP levels. In 6 months, IL-6 concentration was found to decrease, however, not fully returning to baseline. K. Kretsos et al. [31] noted elevation of total IL-6 (the sum of free IL-6 and OKZ-bound IL-6, OKZ/IL-6) in plasma, proportional to OKZ doses, in male healthy volunteers. After just a single administration of this agent IL-6 concentrations gradually increased, reaching plateau by Day 15, and staying at plateau up to Day 99 of follow-up. That was not accompanied by changes in IL-6R or gp130 concentrations.

One of the possible reasons for a significant elevation of IL-6 levels is the high rate of cytokine clearance from circulation, relative to the clearance of IgG antibodies, which OKZ belongs to. Therefore, elimination time of OKZ/IL-6 complexes are far longer, compared to endogeneous IL-6. As such simplexes and complexes cannot be distinguished using conventional assays, probably at the study initiation those figures reflect free IL=6 concentration, whereas the measurements done 3 months later represent total concentrations [13, 31]. However, such hypothesis is yet to be confirmed. We plan to investigate the concentration of this marker over time and present results in subsequent publications.

Furthermore, a post hoc analysis was performed: for 12 months patients were followed up to exclude AEs with delayed onset, as high IL-6 may contribute to cardiovascular, metabolic and infectious diseases etc. No significant AEs, abnormalities in blood or urine tests were found over that period. In addition, all patients reported good clinical response maintained for 6-9 months after OKZ discontinuation.

Conclusion. Therefore, results of this study have shown that OKZ improves all clinical symptoms of OA in patients with inflammatory OA phenotype: effectively reduces pain, stiffness, improves function of joints, quality of life and global health assessment. Treatment resulted in rapid symptomatic improvement, with sustained response (maintained for 6-9 months after the end of treatment).

The study was explorative, has limited sample size and statistical power; therefore, in future it would be particularly important to investigate the economic outcomes and, most importantly, the safety and efficacy of OKZ in patients with inflammatory phenotype.

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