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Research Article

Rheumatic Diseases

Treating Rheumatoid Arthritis by Genetically Engineered Biological Drugs: A Case Study.

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Abstract: The current modern treatment for Rheumatoid Arthritis is the genetically engineered biological drug rituximab. This drug helps to low the active rheumatoid arthritis. The aim of the study is to find and evaluate the clinical efficacy of rituximab . We present our own clinical observation of rituximab use in RA treatment of a female patient. We made the clinical assessment of the patient's condition with the use of clinical, laboratory and instrumental methods. We made diagnostics with the use of the ACR/EULAR (American College of Rheumatology/European Alliance of Associations for Rheumatology) criteria. ESR, concentration of C-reactive protein, IgM of rheumatoid factor, antibodies to cyclic citrullinated peptide were determined. In 2007 the patient was diagnosed RA. She received the treatment with methotrexate, metipred, sulfasalazine, dexamethasone, cyclophosphamide, leflunomide, diprospan, non-steroidal anti-inflammatory drugs (NSAIDs). There was no effect. She had the total right & left knee joints arthroplasty. In 2009, according to blood tests she had: ESR according to Westegren is 90 mm/h, antibodies to cyclic citrulline-containing peptide (AB-CCP) is 500 U/ml, CRP 121.3 mg/l, RF 125.7 IU / ml. She had the diagnosis of rheumatoid arthritis, seropositive, grade 3 activity according to the DAS activity index 28 = 6.11 points with extra-articular manifestations (rheumatoid nodules) late stage, erosive (radiologically stage III), AB-CCP (+), FTS III. She started to receive rituximab therapy. Due to the durable inflammation, the secondary amyloidosis has started. At the same time the secondary systematic osteoporosis has started. We continued the rituximab therapy & zolendronic acid. The RA activity was low (according to the DAS index 28 = 2.95 points). In our study we found that the genetically engineered biological preparation (GEBP) rituximab is effective in the rheumatoid arthritis modern therapy.

Keywords: rituximab; amyloidosis; rheumatoid arthritis, genetically engineered biological drugs (GEBP), osteoporosis

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1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints of unknown etiology, which has a diverse clinical course, characterized by progressive destruction of synovial joints with degradation of cartilage and bones. Over the past 1-2 decades, the paradigms for the treatment of rheumatoid arthritis (RA) have sharply shifted from the initial treatment of non-steroidal anti-inflammatory drugs (NSAIDs) to the subsequent prescription of synthetic and biological disease-modifying antirheumatic drugs (sDMARDs and bDMARDs).We start RA treatment immediately after the RA diagnosis. The specialists recommend RA treatment according to the European League Against rheumatism (EULAR). The scientists published the first EULAR guidelines for the treatment of RA in 2010. According to the 2013 & 2016 recommendations, the doctors changed the treatment additions. The therapy goal is the disease remission. The doctors use the methods to achieve the goals. The 2019 EULAR guidelines[1] for the treatment of RA drew attention to non-pharmacological therapies. Their ancillary methods considered to ensure the best treatment result.[1] Doctors choose pharmacotherapy method taking into account the activity of the disease, the safety of treatment, the presence of concomitant diseases and the dynamics of the progression of structural damage. Disease modification includes amelioration of the signs and symptoms of a disease; improvement of physical functions, quality of life, social and work performance; and, most importantly, inhibition of the onset and / or progression of structural damage to cartilage and bone.[2-4] The biological therapy methods have revolutionized the treatment of rheumatoid arthritis (RA). The impact on the key components of the immune system can effectively suppress the pathological inflammatory cascade that leads to the symptoms of RA and the subsequent destruction of the joints. We know five molecular target families (tumor necrosis factor (TNF), interleukin-6 (IL-6), CD80 / 86, CD20, and Janus kinase (JAK)). The scientists have researched the drugs for each of these molecules. We should correct the drug therapy every 3 months. Up to 50% of patients who receive a new basic drug treatment stop taking it after 12-18 months. It is due to insufficient efficacy or unwanted phenomena.[5, 6] A significant number of patients (about 20% - 30%) are refractory to all existing treatment options, so there is a need to develop new treatments. Patients need to be prescribed drugs with different mechanisms of action to eliminate RA heterogeneity. They should receive the several consecutive treatment regimens throughout their lives. Patients with rheumatoid arthritis (RA) with poorly controlled, long-term course of the disease and with extra-articular manifestations are at risk of developing various complications such as amyloidosis, osteoporosis, etc. Patients' quality of life deteriorates; there are signs of disability, social dysfunction already at working age. The RA patients with complications form the risk group. The RA complications are amyloidosis, osteoporosis and others. The RA patients' life quality get worse. There are signs of disability, social dysfunction already at working age. Osteoporosis is a chronic disease with an increased risk of fractures. Patients with rheumatic diseases are at greater risk of developing osteoporosis. Systemic osteopenia occurs in the early stages of RA even before the onset of the disease[7]. Moreover, the risk of developing osteoporosis (OP) in RA is associated with the duration and severity of the disease. RA patients' disease depends on the age and gender.[8] Glucocorticosteroids (GCS) stop RA activity. They are effective in RA treatment. At the same time, they lead to bone fractures. There are different complications while glucocorticosteroids therapy.[9] Biphosphanates are the drugs for the osteoporosis prevention. Glucocorticoid treatment induces osteoporosis in RA subpopulations. The drugs have proven to be effective in preventing fractures[10] and have an acceptable safety profile.[11]In addition, a drug such as zoledronic acid provides protection against the development and progression of structural damage in RA when used together with cytostatics.[12] Amyloidosis is a protein clotting disorder in which toxic, insoluble aggregates of Fibrillar Amyloid-β Binding Proteins are formed, which gradually disrupt the structure and function of tissues. Amyloidosis can be acquired (secondary) or hereditary. The disease can be localized or systemic. The incidence of amyloidosis in RA patients varies from 11% to 29%, depending on the population and diagnostic strategy.[13-16] It is necessary to screen for amyloidosis in systemic connective tissue diseases. In amyloidosis dynamics, there are latent (hidden); proteinuric, nephrotic and azotemic stages. A morphological study is used for the amyloidosis diagnosis. The specialists make a biopsy of the mucous and submucous layers of the rectum. Amyloid reveals in 70% of cases. The specialist colours the biopsy material with Congo red followed by polarized light microscopy to test for birefringence. When conducting a study, the type of amyloid is determined[17, 18]. Secondary AA amyloidosis is a late and serious complication of poorly controlled chronic inflammatory diseases. Its result is an overproduction of acute phase serum amyloid' protein A (SAB). Amyloid AA fibrils are composed of AA proteins. The N-terminal fragment of SAB contains AA proteins. Hepatocytes produces most of the SABs in plasma. Hepatocytes produce amyloid by cytokines. The regulated cytokines are interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF). The tumor necrosis factor circulates in blood. TNF-α factor rises in acute inflammation and remain stably high in chronic inflammation.[19-21] Seropositive RA with a poorly controlled, long-term course of the disease with extra-articular manifestations are at risk of developing AA amyloidosis.[17,18] The proposed treatment for AA amyloidosis secondary to chronic inflammatory diseases is to suppress the activity of the disease.[8] Recently, therapeutic approaches focused on therapy with tumor necrosis factor α (TNF-α) inhibitors or Tocilizumab. They allow achieving significant clinical improvement and partial destruction of AA amyloid deposits in RA patients.[19-24]The genetically engineered biological drug (GEBP) rituximab, an anti-CD20 monoclonal antibody. It is an effective treatment for patients with severe active RA. The doctors prescribe Rituximab in cases of inadequate response to disease modifying drugs (DMARDs) and TNF-α inhibitors. The scientists point to rituximab's effect for RA patients' secondary amyloidosis.[25-30] The aim of our study is to evaluate the clinical efficiency of the genetically engineered biological preparation (GEBP) rituximab in rheumatoid arthritis treatment.

The objectives of the study are:

1. To make the RA diagnostics with the help of clinical, laboratory and instrumental methods using ACR/EULAR diagnostic criteria.

2. To use the biochemical analyses methods including C-reactive protein, erythrocyte sedimentation rate

(ESR), IgM of rheumatoid factor, and cyclic citrullinated peptide antibodies for the RA patients' condition monitoring using the different drugs treatment.

3. To use the modern diagnostic methods including MRI & other instrumental diagnostic methods.

4. To prove the effectiveness of the genetically engineered biological preparation (GEBP) rituximab in the rheumatoid arthritis modern therapy.

Earlier , we have examined 7 patients with a reliable diagnosis of rheumatoid arthritis (RA) complicated by amyloidosis. For diagnosis, the ACR/EULAR criteria (American College of Rheumatology/European Alliance of Associations for Rheumatology) of 2010 were used, observed in the rheumatology department of the Budgetary Institution "Republican Clinical Hospital" of the Ministry of Health of Chuvashia, most of whom were middle-aged, with a long course of the disease , seropositive for IgM rheumatoid factor (RF) and antibodies to cyclic citrullinated peptide (ACCP), with high activity of the inflammatory process according to the activity index DAS 28, II or III radiological stage, II-III functional class (FC). In total, we examined seven patients with the RA diagnosis complicated by amyloidosis. For diagnosis, we use the ACR/EULAR criteria 2010 (American College of Rheumatology/European Alliance of Associations for Rheumatology). We observed the patients & prescribed the treatment in the rheumatology department of the Budgetary Institution "Republican Clinical Hospital" of the Ministry of Health of Chuvashia. Most of the patients were middle-aged. RA patients were with a long course of the disease. The patients had seropositive for IgM rheumatoid factor (RF) and antibodies to cyclic citrullinated peptide (ACCP). The RA patients had the high activity of the inflammatory process according to the activity index DAS 28, II or III radiological stage, II-III functional class (FC). Before starting therapy with genetically engineered biological agents, patients received methotrexate as a basic anti-inflammatory drug, from 15 to 20 mg per week for more than 3 months. In addition, they received various non-steroidal anti-inflammatory drugs on demand and glucocorticoids from 10-20 mg / day in terms of prednisolone without sufficient therapeutic effect.

2. MATERIALS AND METHODS

In this article, we describe a clinical case of rheumatoid arthritis complicated by rectal amyloidosis. The laboratory specialists determined ESR by the standard international Westergren method (norm ≤30 mm/h). The laboratory specialists measured serum concentrations of C-reactive protein (CRP), rheumatoid factor (RF) IgM by immunonephelometric method using a BN ProSpec analyzer (Siemens, Germany). We used the method of a highly sensitive latex-enhanced test (sensitivity 0.175 mg/l) to assess CRP levels. The value of CRP in blood serum ≤5.0 mg/l corresponded to the norm. We acted according to the manufacturer's instructions. The RF IgM norm concentration was 15.0 IU/ml. We determined the quantity of ACCP in blood serum. We used for ACCP diagnostics enzyme immunoassay commercial reagent kits (AxisShield, UK; upper limit of normal 5.0 U/ml).

3. RESULTS OF OUR OWN CLINICAL RESEARCH

We present our own clinical observation of rituximab use in RA treatment. In September 2007, female patient M. at the age of 38 (born 1969) (Cheboksary, Russia) first came to see a rheumatologist. She applied with wrist joints pain complains (according to VAS 5-6 points). She had 2-3-metacarpophalangeal joints pain and the proximal interphalangeal joints hand pain. She had the right knee joint pain and the left knee joint swelling. She suffered from joints' stiffness all day long. We wanted to verify the diagnosis and select the basic therapy. She was hospitalized in the rheumatology department of the Republican Clinical Hospital of the Ministry of Health of Chuvashia. Based on the examinations' results, we made the clinical diagnosis: "rheumatoid arthritis, seropositive, activity 3, stage I, FDJ II (functional deficiency of the joint)". Prescribed basic therapy with methotrexate at a dose of 10 mg per week and metipred 8 mg / day under the control of analyzes. In July 2009, she hospitalized to the rheumatology department of the Budgetary Institution "Republican Clinical Hospital" of the Ministry of Health of the Chuvash Republic. She had the activity of the disease: pain (according to VAS 6-7 points) and swelling in the proximal interphalangeal, metacarpophalangeal, wrist, knee, joints and high laboratory activity (increased ESR up to 65 mm / h, CRP 35 mg / l). In the hospital, sulfasalazine at a dose of 2g/per day replaced methotrexate. Pulse therapy No. 3 (dexamethasone 12 mg and cyclophosphamide 200 mg) was carried out. Sulfasalazine was ineffective. In December 2009, we canceled sulfasalazine. The patient retained articular syndrome and an increase in ESR up to 50 mm / h. We prescribed leflunomide 20 mg / day. We recommended continuing taking GCS (metipred 8 mg / day, per os). There was no positive dynamics against the background of treatment. While the hands joints pain and the knee joints pain (according to VAS 5-6 points) worried the female patient. Functional insufficiency of the joints increased. The radiographic picture of the hands corresponded to stages II-III of the disease. The patient received treatment up to 2-3 times a year in the rheumatology department. There she received pulse therapy (dexamethasone 12 mg and cyclophosphamide 200 mg No. 3-5) and intra-articular injection of diprospan 40 mg (No. 1-2 times a year) into the knee joints. Her synovitis persisted. Since December 2007, the patient developed persistent knee joints pain (according to VAS 6-7 points). NSAIDs did not help her. MRI of the knee joints revealed aseptic necrosis. Necrosis was a complication of steroid therapy. The patient went for the consultation to the traumatologist of the Federal Center for Traumatology, Orthopedics and Endoprosthetics of the Ministry of Health of Russia (Cheboksary). The specialists recommended her the knee arthroplasty. In August 12, 2008, she had the total arthroplasty of the right knee joint. In April 29, 2009, she had the total arthroplasty of the left knee joint. The postoperative period had no complications, but synovitis persisted. She continued to take metipred 6 mg/day, leflunomide 20 mg/day, NSAIDs (situational). Considering the ineffectiveness of the basic therapy and the progression of the functional insufficiency of the joints in November 2009, the patient hospitalized at the Research Institute of Rheumatology named after V.A. Nasonova (Moscow, Russia) for treatment correction. According to blood tests, ESR according to Westegren is 90-70-28 mm/h, antibodies to cyclic citrulline-containing peptide (AB-CCP)> 500 U/ml, CRP 121.3 mg/l, RF 125.7 IU / ml (Table). She started to

receive the treatment with rituximab. She was discharged from NIIR RAMS in satisfactory condition with a diagnosis of rheumatoid arthritis, seropositive, grade 3 activity according to the DAS activity index 28 = 6.11 points with extra-articular manifestations (rheumatoid nodules) late stage, erosive (radiologically stage III), AB-CCP (+), FTS III.

Table 1: Dynamics of laboratory parameters in the patient in the dynamics of pharmacotherapy

Indicators	Stages of treatment			
	2009	2009 after basic therapy with Methotrexate, glucocorticoids, Leflunomide	2010 onset of Rituximab therapy	2021 against the background of Rituximab therapy
Erythrocyte sedimentation rate, mm/h	65	90	40	5
C-reactive protein, mg/l	35	121.3	44	5
Rheumatoid factor, IU/ml	1205	125.7	9.5	6
Cyclic citrullinated peptide antibodies, Units/ml	520.2	500.1	477.6	440

She had the total arthroplasty of the right knee joint (2008) & left knee joint (2009). In April 2010, the Medico-social Board of Review recognized her as a disabled person of the III group. In June 2010, she was hospitalized at the Research Institute of the Russian Academy of Medical Sciences. Repeated administration of rituximab No. 2, treatment tolerance was satisfactory. The doctors cancelled the GKS (glucocorticosteroids) treatment. In April 2011, she was hospitalized at the Research Institute of the Russian Academy of Medical Sciences for the correction of therapy and determination of management tactics. On admission, the patient was in a moderate condition, nutrition was low, height 163 cm, weight 49 kg, BMI 18.4 kg/m2. She had soreness and swelling in the area of the wrist joints, II-III metacarpal phalangeal joints. The patient had III-IV proximal interphalangeal joints on the right hand, III-IV proximal interphalangeal joints on the left hand. She had rheumatoid nodules, hypotrophy of the interosseous muscles and ulnar deviation. Symptom of transverse contraction of the hands was positive on both sides. The patient had deflection of the knee joints, more pronounced in the left joint due to exudative-proliferative changes. The patient's RA accompanied by knee joints' movement restriction. She had postoperative scars on the anterior surface. The female patient had the deformation of the metatarsophalangeal joints of the feet with subluxation, hallux valgus I of the metatarsal phalangeal joints of the feet. Her heart rate was 74 beats/min, stable hemodynamics, BP 120 /70 mm Hg. The results of the examination revealed anemia (hemoglobin 89 g/l), a decrease in the level of serum iron 3.5 µmol/l, ESR 40 mm /h. The Urine analysis showed the relative density decrease until 1005, the reaction was acidic, there were no erythrocytes, leukocytes 0-1 in the field of view, no protein. The doctors made the immunological parameters. We found out negative result for cryoprecipitation reaction, CRP 44.0 mg /L (normal 0.0-5.0 mg /L) (Table 1). Antibodies to dsDNA 0.1 U /ml (normal 0.0-20.0 U/ml), ANA (Hep-2) 1 /160 (norm <1 /160), rheumatoid factor 9.5 IU / ml (norm 0.0-15.0 IU /ml), AB-CCP 477.6 U/ml , IgG 8.8 g / l (norm 8.0-17 g/l), IgA 1.8 g/l (0.85-4.5 g/l), IgM 1.8 g/l (0, 6-3.7 g/l). ECG sinus rhythm was 83 bpm. The vertical position of the electrical axis of the heart. EGD: endoscopic picture diagnosed superficial antral gastritis. The specialists made rectoromanoscopy & took the biopsy of the rectal mucosa. Histological examination of a biopsy specimen of the rectal mucosa revealed the minimum masses of amyloid. Densitometry showed bone mineral density (BMD) in L1-L4 (Z = + 0.6SD): in Neek (Z = -2.1 SD), in Total of the proximal femur (Z = -2.6 SD). We made the X-ray of the hands and distal parts of the feet. The result was an X-ray picture of stage III-IV rheumatoid arthritis (RA). We noted a negative X-ray picture since 2010. Chest x-ray revealed lungs without visible focal and infiltrative changes. Mantu test showed negative result. Ultrasound of the abdominal organs, kidneys demonstrated diffuse changes in the liver. Kidneys' ultrasound revealed that her kidneys located typically, the contours are even. The right kidney was 113 × 54 mm (norm 120 × 60 mm); the left kidney was 97 × 48 mm (norm 120 × 60 mm). The depth of parenchyma of the right kidney was 21 mm; left kidney parenchyma was 18.5 mm. The kidneys' structure did not change. The pelvis did not dilate. The right kidney's cups are dilated to seven mm. Concretions did not detected. There were single microliths. Echo CG is an additional chord in the left ventricular cavity. Ultrasound of the knee joints showed that ultrasound signs of synovitis from two sides were against the background of endoprosthesis. Ophthalmologist made the consultation. The doctor diagnosed the posterior capsular Cataract & retinal angiopathy. We made the clinical diagnosis: seropositive rheumatoid arthritis, late stage, activity I according to DAS 28 index 6-2.9 points, erosive (X-ray stage III-IV) with visceral manifestations (rheumatoid nodules in history), AB-CCP (+). The female patient had several Complications. Such as functional class III, the latent stage of the secondary amyloidosis, systemic osteoporosis, anemia of chronic inflammation. We diagnosed Concomitant diseases. There were Total arthroplasty of the right knee joint (2008), total arthroplasty of the left knee joint (2009) due to aseptic necrosis. The patient received the treatment: leflunomide 20 mg/day; pulse - therapy Solu-medrol 250 mg i.v. No. 2; rituximab 500 mg i.v. in physiological saline 500.0 ml; calcium D3 per os; aclasta 5 mg i.v. No. 1. We noted the positive dynamics: a decrease in pain syndrome (according to VAS 3-4 points). DAS 28 showed on admission - 6.11 points, upon discharge from the hospital - 5.55 points. A rheumatologist observed the patient after the treatment at the place of residence. She followed a diet rich in calcium; she did exercise therapy every day. The patient performed isometric exercises and used instep supports when walking. The patient followed the doctor's recommendations. She continued to take the drugs: rutuximab 500 mg No. 2 intravenously according to the scheme in a hospital at the place of residence & leflunomide 20 mg/day. During the treatment she had the control of blood tests - bilirubin, AST, ALT, alkaline phosphatase, creatinine, complete blood count,

general analysis of urine. We canceled the drugs for 7-10 days during the patient's infected process. Patient received antisecretors during NSAIDs treatment. The RA female patient's bone mineral density decreased and secondary osteoporosis formed. The patient has been prolonged antiresorptive therapy of osteoporosis with bisphosphonates. She receives zoledronic acid 5 mg/100 ml 1 time/12 months, in combination with combined calcium preparations (1000 mg/day) and vitamin D3 (800 IU/day). Since 2012, the patient has no data for high RA activity. She got the basic therapy. We registered a positive trend: the RA activity assessed according to the DAS index 28 = 2.95-3.12 points. There is no anemia of chronic inflammation. Radiographs of the hands show signs of stage III-IV RA. Since 2012, the patient underwent an annual biopsy of the rectal mucosa and histological examination of a biopsy of the rectal mucosa for amyloid. In 2015, we made the biopsy test of the rectal mucosa. We did not identify the presence of amyloid. According to the results of the examination in May 2021, the indicators of the functional state of the liver and kidneys are within the reference values. In the complete blood, count ESR 5 mm/h (Table). Her biochemical blood tests showed alkaline phosphatase 70 U/L (norm 35-105 U/L), calcium 2.43 mmol/L (norm 2.15-2.5 mmol/L), phosphorus 1.12 mmol/L (norm 0.81-1.45 mmol/L). Her glomerular filtration rate according to CKD-EPI was 86 ml/min. RF 6 U / ml. The blood study showed the content of 25 -hydroxyvitamin D 27.67 ng /ml. Kidneys' ultrasound test result showed that the kidneys are typically located. The contours are smooth. The right kidney is 114 × 54 mm (normal 120 × 60 mm), the left kidney is 99 × 48 mm (normal 120 × 60 mm). The kidneys' parenchyma is normal - 21 mm on the right, 18.5 mm on the left. The kidneys' structure is not changed, the pelvis is not dilated, the cups are dilated on the right kidney to 7 mm. We made biopsy of the rectal mucosa. Histological examination of a biopsy test of the rectal mucosa showed no amyloid. We made DXA. We found BMD = 1.408 g/cm2 in lumbar spine (L1-L4). It accounts for 118% of peak bone mass (T-score = -2.5 SD). We found Z-score = -1.5 SD that is 78% of population bone mass. In comparison with the study dated December 5, 2019, an increase in bone mineral density (BMD) by 2% in the spine, an increase by 0.3% in the proximal left femur. The general condition is satisfactory. Objectively, the skin is clean and warm. Subcutaneous fat is poorly developed. No peripheral edema. The skin is clean, warm, normal color, moisture and elasticity. She walks independently, without additional support. Visually, the area of the left and right knee joints is not changed. Minor deformity of the left knee joint. Postoperative scars without signs of inflammation. There are no local hyperemia, hyperthermia, signs of keloid formation. Movement in the knee joints: flexion 110, full extension (0). On examination of the right foot, the metatarsophalangeal joints are moderately deformed. She has the deformation in peripheral joints due to proliferative changes, accompanied by restriction of movement in them. She has the hypotrophy of the interosseous muscles of the hands. Compression force of brushes is 75%. The patient has the deformation of the metatarsophalangeal joints of the feet with subluxation. Symptom of lateral contraction of the hands is negative on both sides.

4. DIAGNOSIS

Rheumatoid arthritis, seropositive, late stage, activity I degree according to the activity index DAS 28 3.1 points with extra-articular manifestations (rheumatoid nodules in history), erosive (radiologically stage III-IV), AB-CCP (+) FC 3.

Concomitant Diagnosis

Total endoprosthetics (TEP) of the right knee joint (2008) & left knee joint (2009).

Complications

Secondary amyloidosis, latent stage. Secondary systemic osteoporosis (against the background of rheumatoid arthritis, intake of cytostatics, glucocorticoids) with a predominant decrease in bone mineral density in the proximal femur (T-criterion "-2.5SD"), stabilization phase. Vitamin D deficiency. Currently, the patient continues drug therapy. We prescribed leflunomide at 20 mg /s, GEBP (rituximab) at 500 mg per injection No 2 no earlier than 6 months after the last injection. Antiresorptive therapy of osteoporosis continues with the use of combined preparations of calcium 1000 mg/day and vitamin D3 800 IU/day; cholecalciferol in a maintenance dose - 4 drops (2000 IU) with control of the level of vitamin 25 (OH) D in the blood; intravenous administration of zoledronic acid (aclasta 5 mg/10 ml) once a year. The patient has a positive dynamics in treatment. Since 2012, we registered a low RA activity (according to the DAS index 28 = 2.95-3.12 points). It indicates the effectiveness of the therapy. Achieved "modification of the disease" in the form of reducing the activity of the disease, alleviating the symptoms of the disease and improving the quality of life, preservation of working capacity. An important achievement in treatment was the absence of further progression of structural damage from the internal organs and destruction of bone tissue (according to DXA densitometry, an increase in bone mineral density by 2% in the spine, an increase in bone mineral density by 0.3% in the proximal left femoral bones). After the treatment, the patient achieved modification of the disease. She had the disease activity reduced. The disease's symptoms disappeared. Her life quality & working capacity improved. The patient had no internal organs' structural damage further progression. She had no bone tissue destruction. We made the DXA densitometry. We found out an increase in bone mineral density by 2% in the spine. We identified an increase in bone mineral density by 0.3% in the proximal left femoral bones.

5. DISCUSSION

Rheumatic diseases represent a wide range of conditions characterized by a long course, inflammation and destruction of various body structures [1-4]. Our patient had a complex RA case. A patient who had an RA long course has received our treatment. She had the pain & stiffness in the joints. Her biochemical analyses showed the inflammation process. So we identified C-reactive protein, erythrocyte sedimentation rate (ESR), IgM of rheumatoid factor. The modern RA diagnostics method is to identify the cyclic citrullinated peptide antibodies. Our steps in diagnostics are the same with the other specialists from other countries.[9,20]At the beginning of the treatment, she received the basic therapy. However, she did not had the improvement. In the conditions of ineffective therapy, the patient developed aseptic necrosis of the knee joints, which necessitated endoprosthetics. The patients with such kind of symptoms should consult orthopedist. It is necessary to consult regularly orthopedists and make an X-Ray. The other

specialists all over the world point the same diagnostic methods in their articles.[7-9] She received the long-term monitoring & the pharmacotherapy. The other scientists also prove the treatment change. [5, 6, 16, 20] The results of the patient's examination showed the presence of laboratory changes reflecting an active inflammatory process. Some scientists point at the ineffective RA treatment with the help of traditional drugs.[14-16.] The specialists suggest the alternative ways of the treatment. [21, 22, 24, 29] Scientists prove the RA patients' complication developments. [7, 9, 14, 15, 27] In the conditions of a prolonged inflammatory process and ineffective pharmacological therapy, the patient developed secondary amyloidosis. The other specialists from abroad also underlines the secondary amyloidosis-forming while the prolonged inflammatory process. [14-19] However, against the background of adequate therapy, the activity of the inflammatory process decreased. During the repeated diagnostic biopsy of the rectum, we found out amyloid elements. The same results of biopsy have the doctors from other countries.[23, 26.] At the next therapy level, we decided to treat the female patient with rituximab. We had the result from our treatment. Rituximab is an effective drug for the patients with severe RA, who previously had an inadequate response to the appointment of disease-modifying drugs. [21, 27, 30] We use the amyloidosis screening method. Other scientists also proved the importance of the screening method.[23-26] Literature data indicates that RA patients develop periarticular osteoporosis at the disease's first stage. Moreover, under the influence of glucocorticoids, calcium washed out from the bone tissue [7-12] & the activity of osteoclasts increases. [7-12] Laboratory and instrumental diagnostics allowed us to detect structural changes in the bone tissue and to prescribe a preparation of zolendronic acid, vitamin D and calcium. She had the osteoporosis. Densitometry showed the bone mineral density (BMD) in L1-L4 (Z = + 0.6SD): in Neek (Z = -2.1 SD), in Total of the proximal femur (Z = -2.6 SD). After zolendronic acid, vitamin D and calcium treatment the bone mineral density (BMD) had increased by 2% in the spine & the proximal left femur had increased by 0.3%. The doctors from other countries mention in their works about the importance of zolendronic acid use.[9-12] The prolonged Rituximab RA treatment decreased the disease's activity. We registered a low RA activity according to the DAS index 28 = 2.95. The specialists prove the high effectiveness of rituximab.[6, 13, 21, 30.] The use of the EULAR recommendation for the treatment of RA makes it possible for the doctors of practical healthcare to optimize and to improve the outcomes of treatment, the quality RA patients' life. The peculiarity of this clinical case is that until 2010 there was no algorithm for treating patients with RA, while the arsenal of rheumatologists was limited to prescribing only such drugs as Methotrexate, Sulfasalazine and glucocorticoids. This introduced certain difficulties to the patients' treatment. The results of the patients' examination showed the presence of laboratory changes reflecting an active inflammatory process. In the dynamics of treatment, we noted normalization of biochemical parameters such as rheumatoid factor, C-reactive protein, erythrocyte sedimentation rate. The presented results are indicative of Rituximab effectiveness in the patient with severe rheumatoid arthritis, which did not respond to therapy with the use of disease-modifying drugs. The RA patients should pass the amyloidosis screening. Timely treatment of osteoporosis makes it possible to avoid bone tissue destruction. The management of patients with rheumatoid arthritis requires an individual approach in using effective pharmacotherapy regimens.

6. CONCLUSION

We have used clinical, laboratory and instrumental methods for the RA diagnostics using ACR/EULAR diagnostic criteria.For the effective results we have used the biochemical analyses methods including C-reactive protein, erythrocyte sedimentation rate (ESR), IgM of rheumatoid factor, cyclic citrullinated peptide antibodies. Simultaneously we had used the modern methods including MRI & other instrumental diagnostic methods. The genetically engineered biological preparation (GEBP) rituximab is effective in the rheumatoid arthritis modern therapy. This RA patient's clinical case is so complex & so meaningful for the practical doctors and scientists. For the RA diagnostics, we used the modern laboratory & instrumental methods, which are available in clinics & hospitals. We treated this female patient for a long term & changed the therapy scheme while the traditional treatment methods were not effective. We recommend to the RA patients making the densitometry & amyloidosis screening. We noticed the clinical rituximab effectiveness. We recommend using the zolendronic acid therapy for osteoporosis to the RA patients.

7. AUTHORS CONTRIBUTION STATMENT

Dr. Zhuravleva Nadezhda Vladimirovna and Dr.Sharapova Olga Viktorovna conceptualized and designed the study, Dr. Gerasimova Liudmila Ivanovna and Dr. Diomidova Valentina Nikolaevna currated the data and prepared the original draft. Dr. Smirnova Tatiana Lvovna, Yastrebova Svetlana Alexandrovna and Dr.Ukhterova Nadezhda Dmitrievna discussed the methodology and analysed the data. Dr. Karzakova Luiza Michailovna and Dr. Arkhipova Anastasia Vladimirovna provided valuable inputs towards designing of the manuscript. All authors read and approved the final version of the manuscript.

8. CONFLICT OF INTEREST

Conflicts of interest declared none.

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