RHEUMATOID ARTHRITIS: A NOVEL APPROACH IN DIAGNOSIS AND TREATMENT

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REUMATOIDNI ARTRITIS: NOVI PRISTUP U DIJAGNOSTIKOVANJU I LEČENJU

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ABSTRACT

The rheumatoid arthritis is chronic disease with progressive course and deteriorations of joints as well as other organs. The pathogenesis of rheumatoid arthritis is characterized with chronic synovitis and inflammation. The main roles in development of rheumatoid arthritis have auto-reactive T cells and inflammatory cytokines, especially tumor necrosis factor α, interleukin 1 and interleukin 6. The management of rheumatoid arthritis has evolved significantly in the past twenty years, especially with introduction new diagnostic criteria by European League for Rheumatoid Arthritis which are very sensitive for early arthritis. The main goal of treating rheumatoid arthritis is to start with therapy in the phase of the disease when destruction of joints can still be prevented. Therapeutic strategies for rheumatoid arthritis involve wide palette of different drugs which can be divided into conventional and biological Disease Modifying Anthirheumatic Drugs. The use of methotrexate in combination with biological drugs provide targeting not only structural changes in rheumatoid arthritis but also and immunological pathways in development of rheumatoid arthritis. These drugs synergistically provide clinical remission and low activity of rheumatoid arthritis in the majority of patients. The uses of biological drugs are limited due their high costs or safety profile. In order to reduce costs and toxicity in the treatment of rheumatoid arthritis, new treat- to –target concept is established. The new class of drugs which modulate signal pathways and activity of tyrosine kinase are under investigations in post marketing surveys in patients with rheumatoid arthritis as in efficacy as in safety issues.

Keywords: *rheumatoid arthritis; conventional Disease Modifying Anthirheumatic Drugs; biological Disease Modifying Anthirheumatic Drugs*

SAŽETAK

Reumatoidni arthritis je hroničnо oboljenje progresivnog toka sa dominantnim oštećenjem zglobova, ali i drugih organa. Patogeneza reumatoidnog artritisa se odlikuje hroničnim zapaljenjem sinovije i postojanjem inflamacije. U razvoju reumatoidnog artritisa najznačajniju ulogu imaju auto reaktivni T limfociti i citokini, posebno faktor nekroze tumora alfa i interleukini 1 i 6. Proces lečenja reumatoidnog artritisa je značajno napredovao u poslednjih dvadeset godina, posebno uvođenjem novih dijagnostičkih kriterijuma od strane Evropske Lige za borbu protiv Reumatoidnog artritisa koji su posebno značajni za detektovanje reumatoidnog artritisa u ranoj fazi. Posebno je značajno započeti sa terapijom reumatoidnog artritisa u njegovoj ranoj fazi kada se oštećenja zglobova mogu sprečiti. U terapiji reumatoidnog artritisa se koriste lekovi koji menjaju tok bolesti, a koji se mogu podeliti na konvencionalne i biološke. Primena metotreksata u kombinaciji sa biološkim lekovima omogućava dejstvo kako na strukturne promene u reumatoidnom artritisu tako i na imunološke mehanizme koji su značajni za dalji razvoj ove bolesti. Ovakva kombinacija lekova omogućava uspostavljanje remisije kod značajnog broja pacijenata obolelih od reumatoidnog artritisa. Primena biološke terapije je limitirana visokim troškovima lečenja i neželjenim dejstvima. Kako bi se redukovali troškovi lečenja i toksičnost ovih grupa lekova, u lečenju reumatoidnog artritisa je uveden novi "treat to target" koncept. Upotreba nove klase lekova u lečenju reumatoidnog artritisa sa ciljnim dejstvom na signalne puteve tirozin kinaze se još uvek ispituje u smislu efikasnosti i bezbednosti u postmarkentiškim istraživanjima.

Ključne reči: *reumatoidni arthritis, standardna terapija reumatoidnog artrtisa, biološka terapija reumatoidnog artrtisa*

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ABBREVIATIONS

ACR - American College of Rheumatology
ACCP -Antibodies against cycled citrullinated peptide
bDMARD-s – biolocical Disease-modifying antirheumatic drugs
CRP- C reactive protein
c DMARD-s – conventional Disease-modifying antirheumatic drugs
DAS28 - Disease Activity Score
DMARD-s - Disease-modifying antirheumatic drugs
EULAR - European League for Rheumatoid Arthritis
ICER - Incremental cost-effectiveness ratio
IL-1 - Interleukin-1
IL-6 - Interleukin-6
IL-8 -Interleukin 8
HAQ - Health Assessment Questionnaire
NICE - National Institute for Clinical Excellence
NSAIL - Non steroidal anti-inflammatory drugs
MMP - Metalloproteinases
MTX - Methotrexate
QALY - Quality-adjusted life year
RA - Rheumatoid arthritis
SAARD - Slowly acting antirheumatic drugs
TNF-α - Tumor necrosis factor - α
VAS - Visual analogue scale
VEGF - vascular endothelial growth factor

INTRODUCTION

Rheumatoid arthritis (RA) is a serious chronic disease which is characterized by persistent synovitis, systemic inflammation, and resence of autoantibodies (particularly to rheumatoid factor and pcitrullinated peptide) (1, 2) . Epidemiological data indicate that RA is one of the most prevalent chronic diseases with inflammatory genesis (3) . The primary targets in development of pathological processes in RA are joints but prevalence of extraarticular manifestations in RA patients is high too which lead to increased level of complications and comorbidities and reducing quality of life in RA patients (4-6). The introduction of biological drugs, especially those which target tumor necrosis factor-alpha have changed the management of RA and in the past decade initiated a novel approach in diagnosis and therapy of RA (1). In this review, we will evaluate the novel approach in diagnosis and therapy in patients with RA.

Epidemiology and clinical manifestations of rheumatoid arthritis

The prevalence of RA is 1% among general population, mostly involving people during their economically productive part of life (3). The prevalence of rheumatoid arthritis is 3 to 4 times higher among the women with rising tendency with aging (4-5). The onset of disease can be acute, but more often RA develops gradually with progressive course, which leads to structural changes of affected joints and surrounding tissues decreasing their functional ability and reducing quality of life of patients with RA (6). Mortality rate and morbidity due to RA are higher than in general population, since patients with RA have increased susceptibility to cardiovascular diseases, lymphomas and other extra-articular manifestations of RA (7). Extra-articular manifestations of RA are presented in 40% of patients with RA and they increase mortality for 3 to 4 times compared to patients without extra-articular complications.

Etiology and pathogenesis of RA

The etiology of RA is partly known (8). Genetic predisposition has an important role in pathogenesis of rheumatoid arthritis. Recent studies have shown that microbiological agents as Parvo viruses could lead to polyarthritis and development of RA, but in small percent of patients (2, 7%) . The other etiological factors are obesity, smoking, heat shock proteins and presence of rheumatoid factor (RF) and/or antibodies against cycled citrullinated peptide (ACCP antibodies). (9, 10). RF is an antibody (IgM and IgA) which binds to Fc portion of IgG and ACCP antibodies are autoantibodies which are directed to citrulinated peptides. (9).

The primary pathological process in RA mainly affects cells of synovial membrane and cartilage. In pathological circumstances which dominate in the pathogenesis of RA, cells of synovial membrane, fibroblast synovial cells and macrophages like synovial cells lose protecting role and transform into joint destroying cells which lead to conditions for development of increased production of proinflammatory cytokines (1, 4, 11, 12). The inflammation process on joints in RA developed due to increased influx of immune cells, especially macrophages, dendritic cells, lymphocytes, neutrophiles, and mastocytes which lead to hyperplasia of cells of synovial membrane (13).

On the surface of inflamed joints, fibroblasts and mononuclear cells contribute to pannus formation, another characteristic of RA which has a significant proteolytic activity and implicates further damage of local tissue (2). Angiogenesis has a substantial role in the pathogenesis of RA too, especially in exacerbation of inflammation process. Cytokines: tumor necrosis factor-alpha (TNF-α) and interleukin 1, 6, and 8 (IL-1, IL-6, IL-8) can be powerful inducers or blockers of angiogenesis. TNF-α, IL-1, IL-6 may increase directly angiogenic activity or they can modulate vascular endothelial growth factor (VEGF) - dependent pathways. TNF-α induces the process of neovascularisation by itself and also trough capillary formulation in process via VEGF activity. IL-6 also enhances the angiogenesis process due to initiation of VEGF production. IL-8 is involved in process of induced activity of transformed synovial fibroblast which leads to induction of angiogenesis due VEGF pathways. In the presence of blockers of these cytokines the level of angiogenesis is decreased. Most of these mediators are targets for biological drugs used in the treatment of RA (1, 14).

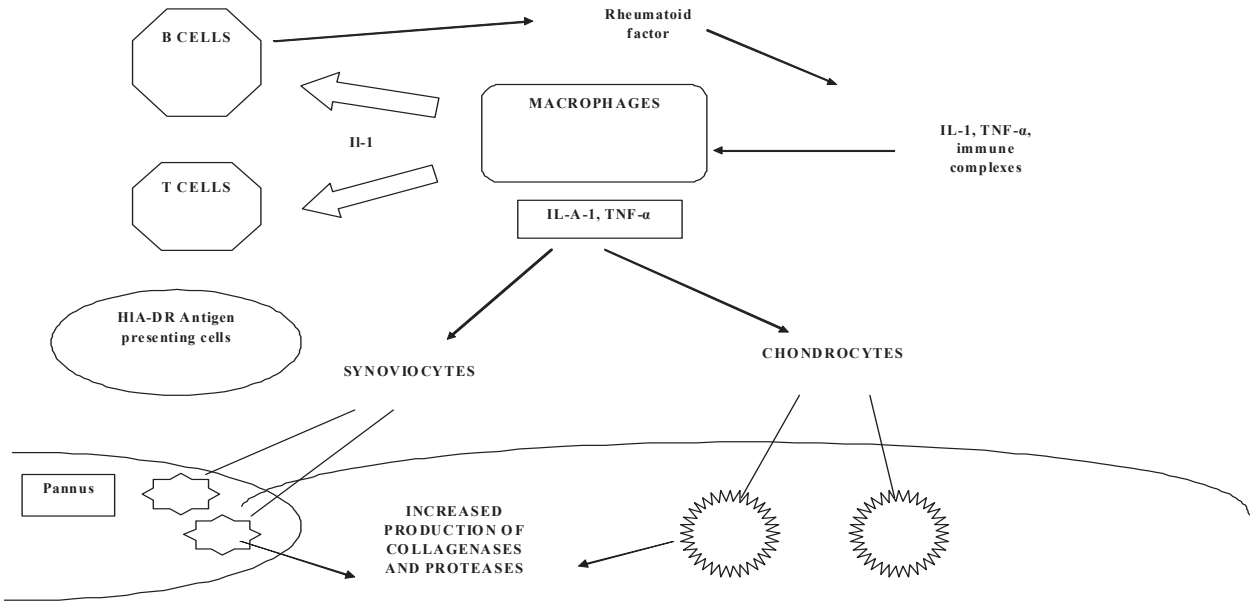

Figure 1. The mechanism of developing synovitis in rheumatoid arthritis

The increased influxes of immune cells in the pathogenesis of RA are regulated by: TNF- α, IL-1 and IL-6 (13). TNF- α has a dominant role in profoundness of inflammation process on synovial membranes and in deterioration of affected joints in RA. The production of these cytokines is result of interaction between antigen presentating cells and CD4- T cells. Antigen presenting cells expose complexes of class II major histocompatibility compex molecules and peptides antigens which induce binding with receptors on T cells. The following step is activation of macrophages with secretion of proinflammatory cytokines (4).

The immune cells and their migration into affected joints in patients with RA can lead to impairment of bone and cartilage tissue around affected joints, not only by cytokine - mediated processes, but also due to effects of metalloproteinases (MMPs) and aggrecanases originating from bone matrix which disturb the balance between anabolic and catabolic processes in the bone tissue. MMPs, especially MMP-s 7 in injured cells cleaves ectodomain of syndecan – 1 which induce releasing of chemokine named KC which than increase influx of inflammatory cells. (16)

Activated fibroblast with accumulated T-cells and B-cells, macrophages and monocytes enhance production of osteoclasts via promotion of receptor activator of nuclear factor κ B ligand (RANKL) T –cells and B-cells and via RANK receptor on macrophages, dendritic cells and proosteoclasts (17).

These newly derived osteoclasts have crucial role in process of bone resorption which leads to progression of inflammatory process of RA in deeper structures of bone.(16).

Clinical manifestations in RA

Since that in RA crucial processes on the synovial membrane are chronic inflammation and its complications, clinically in patients with RA dominate pain, stiffness, joint swelling, movement difficulty, but also systemic inflammatory changes such as fever, fatigue, anemia, as well as changes in laboratory parameters: elevated erythrocyte sedimentation rate, elevated reactive protein C (CRP), hypergammaglobulinemia and elevated levels of various auto antibodies (18). Clinical manifestations of RA are the result of intense inflammation process on joints and it is presented mainly as fluctuated swelling of joints primarily on hand and wrist joints, joints of the feet, or on the larger joints such as joints of the cervical spine, shoulders, knees and hips which result with different level of disability in patients with RA (2). In patients with RA special concern is needed due to extra-articular manifestations of this disease, especially in patients with poor response on therapy. Extra-articular manifestations include multiorgan diseases as pulmonary, ocular, vascular, cardiac, neurological and cutaneous are. These extra-articular manifestations involve the presence of rheumatoid noduli on different organs or developing inflammation processes on different organs in patients with RA. The special concern in patients with RA are needed due to higher incidence of co-morbidities on cardiovascular system (heart failure, myocardial infarction, stroke, hypertension), higher incendence of cancer (lymphoma, lymphoproliferative disease, lung cancer, skin cancer), infections and other diseases (depression, osteoporosis, psoriasis...) (2, 4).

Diagnostic criteria for rheumatoid arthritis

In 1978, American College of Rheumatology (ACR) established criteria for diagnosis of RA. According to these criteria during clinical assessment, four of the following criteria must be presented in patients: morning stiffness which lasts at least one hour, arthritis with edema in three or more joints confirmed by specialist, arthritis on joints

of a hand (with edema more than in one joint), symmetric arthritis, rheumatoid skin noduli, positive value of laboratory tests for rheumatoid factor, radiologically confirmed typical findings for RA. All criteria, except the last two last, must last at least six weeks in moment of clinical assessment of RA (19-21).

In 2010, European League for Rheumatoid Arthritis (EULAR) has recommended an amendment of ACR criteria for RA, since these criteria lack in sensitivity for early phase of RA. According to this amendment, for diagnosis of RA, a new scale is established where score should be six or more than six, with included criteria such as involvement of the joints, the positive values of serological analysis, the presence of elevated levels of laboratory tests C reactive protein and erythrocyte sedimentation and duration of symptoms (21). These recommendations are especially related to newly diagnosed patients with RA with clinical presentation with synovitis and edema within one joint and in patients with synovitis where etiology is not determined (21).

Disease activity score (DAS) was designed in 1983, for purpose of improvement of former criteria for measuring activity of RA - index of RA. Nowadays DAS is a gold standard for estimating activity of RA, with values of low and high activity of RA. This score is the result of formula which obtains number of joints with edema (with examination of 28 joints: joints of shoulders, elbows, wrists, knees, metacarpophalangeal joints and proximal interphalangeal joints), value of blood sedimentation and general health state of patient according to visual analogue scale (VAS) (22, 23). The range of DAS 28 is if value of disease activity score is higher from 5, 1, then RA has high activity, value of DAS 28 between 3, 2 and 5, 1 RA has moderate activity and RA has low activity if the value of DAS 28 is between 2, 6 and 3, 2. EULAR has developed criteria for estimating RA patients' response on therapy which are based on DAS 28 criteria. Patient's response to therapy can be considered good if change of value of DAS28 is significant and disease activity is low. According to these EULAR criteria, there are three patterns of response to therapy among patients with RA: good response, moderate response and no response to therapy. Decreasing of value of DAS 28 for 0, 6 indicates that patient with RA has no response to therapy, while decreasing of value of DAS 28 for 1, 2 and more indicates on moderate and good response. If value of DAS 28 is less than 2, 6, then patients with RA are in remission (24).

Rheumatoid arthritis decreases the ability of patients for management of everyday activity, which leads to a decrease of quality of these patients. Health Assessment Questionnaire involves functional ability of patients in several domains: inability, pain and discomfort, adverse reactions of drugs and economic sphere of treating RA. Each domain of HAQ is assigned with a grade, summarizing patient's answers clinicians obtain from HAQ score and value they got, which can vary from zero to three, where zero represent state without disability and three represents state of full disability (25-27).

Laboratory parameters in patients with rheumatoid arthritis can indicate presence and course of inflammation process and can be useful for assessment of development of RA and for monitoring of patients' response to therapy. Increased values of erythrocyte sedimentation rate, level of fibrinogen, C reactive protein and rheumatoid factor are repercussion of induced effects of TNF α, IL-1, IL-6 partly on immune cells, partly on liver (28). The more significance antibodies for RA are those directed against cycled citrullinated peptides (ACCP antibodies). ACCP antibodies are more specific for patients with RA and their presence is better indicator for poor response on therapy and progressive joint deteriorations. The results of recent clinical studies indicate that in synovial tissue of ACCP antibodies positive RA patients dominate lymphocytes and in ACCP antibodies negative RA patients synovial membrane are changed due to fibrosis. Circulating ACCP antibodies can indicate on pre-rheumatoid arthritis, since it can be detected in patients with RA 10 years before diagnosis. The presence of ACCP antibodies indicate on increased joint deteriorations and on low remmision rate. The values of ACCP antibodies and RF decrease due to effects of therapy, but patients with RA rarely became ACCP antibodies negative comparing to RF whereas seropositive RF patients more frequently convert to seronegative RF patients (4, 10).

Therapeutic strategies in patients with rheumatoid arthritis

The main aim of therapy in rheumatoid arthritis is to prevent spreading of chronic inflammation process and to ensure protection of deteriorated joints from further damages (15, 29).

The idea of early introduction of therapy in patients with RA was substantial for better management of RA, but the most crucial step in historical development of therapy for RA was introduction of biological drugs (30-33).

Modern concept of treatment of rheumatoid arthritis involves achieving a state of remission in patients without evidence of inflammation and joint damage. In broad terms, the goals of therapy can include reduction in disease activity, reduction of pain, maintenance of functional status of the joints and preservation of working ability, but also the ability for daily activities of patients. Since the nature and course of molecular mechanisms responsible for symptoms of synovitis in chronic inflammation are different from the mechanism which is responsible for the structural deterioration of joints, therapy of rheumatoid arthritis should affect both pathophysiologal processes (15).

Disease-modifying antirheumatic drugs in therapy of rheumatoid arthritis

"Go low go slow" concept based on use of physical therapy, non pharmacological treatment and low doses of non steroidal anti-inflammatory drugs (NSAIL) was abandoned during the eighties of the last century. Despite the use of NSAIL in patients with RA which provides re-

duction in symptoms, recommendations for treatment early phase of RA indicate that Disease-modifying antirheumatic drugs (DMARD-s) that affect the course of the disease should be the first choice treatment (35-37). DMARD-s are administered mainly orally and in lower doses they provide anti-inflammatory effects, prevent further deteriorations of affected joints and their surrounding tissues so they can be used for management of RA for longer period. Disease-modifying antirheumatic drugs include two major classes of drugs: synthetic and biological drugs. Further synthetic DMARD-s can be divided into two groups of drugs: conventional synthetic DMARD-s and targeted synthetic DMARD-s. The targeted synthetic drugs, like tofacitinib and baricitinib are janus kinase inhibitors which can modify the specific reaction in propagation of inflammation. Conventional synthetic DMARD-s were introduced in the treatment of RA trough positive experience but their mode of action in RA has still been unclear (38).

The earlier use of conventional synthetic DMARD-s provides better control of disease activity in patients with RA and improves effects of combination of conventional synthetic DMARD-s and biological drugs. Conventional synthetic DMARD-s applied in patients with RA decrease swelling of joints, reduce pain, lower the parameter values of acute phase of inflammation and improve joint function (21, 39-45).

Conventional synthetic DMARD-s

Conventional synthetic DMARD-s include the broad spectrum of drugs: metotrexate, glucocorticoids, sulfasalazine, leflunomide, hydroxychloroqine, gold therapy.

EULAR criteria for management of RA with synthetic DMARD-s and biological drugs recommend that therapy of RA should be initiated with methotrexate with a low dose of glucocorticoides (46).

Methotrexate (MTX) is a gold standard in the therapy of RA which has been used in the last 25 years. The mechanism of action of MTX is directed on dihydrofolate reductase which MTX competitively and irreversibly inhibits with disabling conversion of dihydrofolate in tetrahydrofolate. By this step, MTX inhibits synthesis of DNA, RNA and proteins in gastrointestinal, medullar and neoplastic cells. The potential antiinflammatory action of MTX can be explained by its blocking of thymidylade synthase which increases intra – and extracellular adenosine activity. By these mechanisms, only part of antiinlammatory action of MTX as its final effects on decreasing of proinflammatory mediators: TNF-α, IL-1, IL-6, metaloproteinases, prostaglandines and adhesion molecules can be explained (47). The dose regimen for MTX in patients with RA for oral or parenteral administration varies from 7.5 to 25 mg per week. The results of numerous studies have shown that the adequate use of MTX in patients with RA provides improvement as in preservation of functional ability of affected joints as well as in prevention of further structural damages (39, 47).

Despite these facts, the effects of MTX in patients with RA may fail due to toxicity or inefficacy. According to guidelines, use of MTX in patients with RA should be followed with associated administration of folic acid (5-15mg per week) or folinic acid (leucovorin in dose 27, 5 mg per week) due to decreasing adverse events (48). The most frequent adverse events are gastrointestinal ones with mild clinical presentations as dyspepsia, nausea, vomiting and abdominal pain. Rarely, severe clinical presentation as hepatic, pulmonary, haematologic, neurological, cutaneous and infectious adverse events can occur during MTX administration. Among hepatic adverse events in patients with MTX therapy, hepatic fibrosis and cirrhosis are most frequent. In order to prevent these adverse effects, special monitoring of liver enzymes (transaminases, gamma-glutamyl transferase, and alkaline phosphatase) is recommended and special concern is needed if these enzymes are higher two or more than two times in patients with MTX therapy as decreasing the dose of MTX and discontinuation of therapy are (47, 48). Chest X-ray should be performed at the beginning and during MTX therapy due to evaluated pulmonary toxicity induced by MTX (interstitial pneumonitis, pulmonary fibrosis, and non-cardiogenic pulmonary oedema). In the interest of prevention of hematological adverse events, patients with MTX therapy should undergo the tests of blood cell counts. Infectious diseases are more common in patients undergoing MTX therapy. Among neurological adverse events due to MTX toxicity headache, dizziness or impairments of speech, vision or cognition are more often. It is recommended that patients with RA treated with MTX should undergo frequent medical testing and supervisions, not only by rheumatologists but also by other specialists. The supplementation with folic acid is another preventive measure for reducing of MTX induced toxicity (48-52). MTX therapy is X category according to Food and Drug Administration and it is not recommended during pregnancy; the treatment with MTX should be determined 1 to 3 months before conception (53).

MTX is indicated as monotherapy or in combination with other drugs in the treatment of RA. (45). The glucocorticoides are indicated as in the early phase of RA as in RA with developed extra-articular manifestations of RA. The dose regimen varies from use of small doses (< 7, 5 mg prednisone or equivalent per day) in the first six months of treatment, use of average doses (10-30 mg per day), use of large doses (>30mg per day) and use of pulse therapy with a dose higher than 250 mg of methylprednisolone per day via infusion (54, 55). The main disadvantages of use of glucocorticoides are adverse drug reactions of this group of drugs, which can be divided into two groups: preventable and non preventable (47). Preventable adverse drug reactions include wide range of impairments: heart failure, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, miopathy, insomnia and mood disturbance. Considering that facts that pathological processes in RA affect bone too, osteoporosis induced by glucocorticoides remains the

most endangering adverse drug reaction due to its decreasing effects on the process of bone formation and increasing effects on the bone resorption. Non-preventable adverse reactions involve infections, cataract, cutaneous modifications, accelerated atherosclerosis, and weight gain (54). For this reasons, crucial recommendations regarding the use of glucocorticoides in RA are that their use should be favorable in settings where their benefit exceeds risks: short term systemic use during relapse of RA, where their effects lead to rapid improvement and local use whenever it's possible (55-57).

Hydroxychloroquine and chloroquine are antimalarial drugs with antirheumatic activity which is directed to lysosomal membranes. These drugs change pH activity of lisosomes and stabilize the membranes of these cell structures which leads to suppression of immune response and activity of cells with dominant role in inflammation process: T cells and granulocytes and their migration. These drugs are mainly used in combinations as triple therapy with MTX and sulfasalazine, since their use as monotherapy has moderate efficacy in patients with RA. The use of these drugs is related to adverse reactions mostly with mild clinical presentations: nausea, anorexia, rash, photosensitivity, while those with severe clinical outcome (irreversible retinopathy) are rare (58, 59).

Sulfasalazine is pro drug, which is trasformed by bacteria in colon into active forms of sulfapyridine and 5-amino salicylic acid. Anti-inflammatory activity of sulfasalazine is related to reduction of the secretion of TNF-α, IL-1 and IL-6, decreasing production of immunoglobulin G and rheumatoid factor by B lymphocytes and to inhibition of T lymphocytes. The dose regimen of sulfasalazine in patients of RA is 2-3 g/day, as monotherapy as in combination with conventional or biological DMARD-s (50, 60-63). The side effects of sulfasalsalazine have mild clinical presentations: nausea, dyspepsia, anorexia, mild damage of liver, rash, itching, photosensitivity, anxiety, headaches, sleep disturbance… The multiform erythema and serious hematological adverse effects as lymphopenia, neutropenia and agranulocytosis are rare during sulfasalazine treatment in patients with RA (63). Treatment of RA during pregnancy with sulfasalazine is mostly safe, but due to its' concentrating in milk, special concern is needed during breastfeeding (64).

Leflunomide is another pro-drug which is converted after first hepatic passage in the submucosal intestinal into active form and that leads to inhibition of dihydroorotate dehydrogenase and decreasing synthesis of enzymes involved in pirimidine synthesis and further to diminishing of activity of tyrosine kinase and nuclear factor (NF)-κB activation. The usual dose for leflunominde is 20 mg per day and it is effective in treatment of RA, as monotherapy as in association with other DMARD-s. Leflunomide is used as effective treatment both in early and late stage of RA leading to improvement, remission and prevention of further structural deterioration. The safety profile of leflunomide is similar of those of MTX (65, 66).

In the treatment of RA, the gold therapy can be used too, since they inhibit cytokine production and decrease the level of mediators of inflammation which leads to suppression of macrophages. But, despite its efficacy, the gold therapy is only used if patients haven't responded adequately to previous treatment, since the presence of its significant adverse reactions (34, 67).

Biological DMARD-s

Since the crucial role of immunopathogenic pathway in development of RA, biological therapy has demonstrated efficacy in prevention as well as in functional and structural deteriorations in patients with RA. Biological therapy in treatment of RA is directed to cytokines such TNF-α, Il-1, IL-6 and these groups of drugs are defined as cytokines inhibitors. The other group of biological drugs, non-cytokines agents are involved via their' mechanism of action in pathways of T-cell co-stimulation blockade, and B-cell depletion and on non-cytokine as CD-20 receptor on B cells (68-70).

The blockade of TNF-α is a potent mechanism of action which is directed to cytokine with a pivotal role in the pathogenesis of RA. These drugs can be administered intravenously (infliximab) or subcutaneously (adalimumab, etanercept, golimumab and certolizumab pegol). Among TNF blockers, the structure of etanercept matches with the structure of TNF receptor, while other drugs operate as monoclonal antibody or its part (40, 48).

Etanercept is a recombinant form of the soluble human TNF receptor, which binds specifically to circulating TNF - α and prevents further proinflammatory role of TNF-α in RA. The use of etanercept in the treatment of RA is indicated in presence of a moderatly severe or severe form of RA where patients have previously responded inadequately to conventional DMARD-s. The usual dose regimen is 50 mg per week (40, 71, 72).

Adalimumab is human IG - 1 monoclonal anti TNF-α antibody, which targets specifically TNF, blocking further interactions with TNF receptor and interfering with reactions which are mediated by this mediator. Adalimumab is indicated as subcutaneous injection in dose of 40 mg every other week in patients with a moderately severe or severe form of RA who have previously an inadequate response to conventional DMARD-s (71, 72).

The other fully human monoclonal antibody which binds TNF – α is golimumab with usual dose regimen of 50 mg per month. Certolizumab is derived from human monoclonal anti TNF-α antibody and it contains only Fab fragment which is covered with polyethylene glycol. Certolizumab is used every two weeks in dose of 200 mg (40, 48).

Infliximab is a chimeric monoclonal antibody which is consisted of parts of human IG1 and variable murine Fv regions. It is the only TNF-α blocker for intravenous administration with dose regimen of 3-10 mg / kg every 4-8 week (40, 48).

The safety profile of biological drugs encompasses increased level of infections, cancer, demyelinating disease,

deterioration of heart disease, allergic reactions and production of anti drug antibodies and anti ds- DNA antibodies (73, 74).

Tocilizumab is biological drug with anti IL-6 effects. It is administered via intravenous infusion in dose of 8 mg/kg once a month. Tocilizumab is used as monotherapy or in combination with other cDMARD-s in patients who didn't respond to the pervious treatment with MTX or anti-TNF therapy. During therapy with tocilizumab, adverse reactions as infections, diverticulis, dyslipidemia, liver damage and neutropenia can occur (75, 76).

Abatacept is the first biological drug whose mechanism of action is involved into modulation of T lymphocyte activity. Abatacept binds to CD80/86 and CD 28 costimulatory factors and via these mechanisms, it decreases activity of T lymphocytes. Abatacept is administered via intravenous infusion in dose regimen of 500-1000mg (at weeks 0, 2, 4 and then once monthly) or as subcutaneous injection in dose of 125 mg per week. The most frequent adverse reactions are increased risk of infections, reduced positive response to vaccines and infusion related reactions. (76-79).

Rituximab is a chimeric monoclonal antibody whose mechanism of action is directed at CD 20. It is administered intravenously in dose of 1000 mg every 6 months who are unresponsive to TNF-blockers. The use of rituximab is indicated in patients with RA who are unresponsive to TNF-blockers. The safety profile of rituximab is more favorable than in other biological drugs especially in patients with RA who have concomitant diseases: multiple sclerosis, lymphoma or latent tuberculosis with contraindications of prophylaxis with isoniasid whereas other biological drugs should be avoided since they can provoke these diseases (40, 45, 80-82) .

The use of biological therapy during pregnancy is disputed, results of recent studies indicate that use of TNF inhibitors does not correlate with conception or teratogenic risk, similar data have been published for tocilizumab and abatacept (83, 84).

Review of effectiveness of different therapeutic strategies in RA

The results of clinical studies which compare MTX and glucocorticoides and MTX and biological drugs in patients with RA haven't shown significant difference in outcomes. In patients with RA, who were treated with glucocorticoides in low doses in combination with MTX better structural protection of affected joints was provided than in the group with monotherapy with MTX (85). After six months of therapy, the dose of glucocorticoides should be gradually decreased and stopped when DMARD-s achieved full effects (85, 86). The clinical outcomes in patients with RA, in studies which compare MTX, sulfasalazine and leflunomide were similar, but MTX remains the core of therapy of RA especially because it optimizes effects of further therapy with biological drugs. In the numerous clinical studies triple therapy for RA (MTX, sulfasalazine and hydroxychloroquine) was compared to monotherapy with MTX, but greater efficacy of triple therapy remains "blured", since in that arm of study glucocorticoides were applied ih higher doses. Further results of clinical randomised studies where lower dose of glucocorticoides was administered in triple- and in mono- therapy group have shown that no significant advantage was detected in the group with triple therapy, but only higher costs and more adverse effects (86, 87). According to ACR guidelines, combination of cDMARD-s is not recommended as early first line therapy in patients with RA due to limitations of numerous clinical studies which investigate use of these kind of therapeutic strategy in RA. But, in patients with RA with low risk of progressive disease and with poor response on MTX adding of other cDMARD-s or switching on other cDMARD-s may be optimal treatment (88, 89). EULAR provides guidelines for treating patients with high disease activity, high values of autoantibodies and RF and early joint damages on radiography; according to these recommendations patients with these characteristics should be switched to the biological therapy in combination with cDMARD-s and glucocortiocides (45).

The results of numerous clinical studies have shown benefits of biological treatment in patients with RA. MTX in combination with TNF inhibitors or with tocilizumab provide clinical remission in 30 – 60% of RA patients (30). The biological DMARD-s accomplishe more significant effects in patients with RA if they are in combination with MTX or other cDMARD-s, especially leflunomide. The results of recent studies indicate that tocilzumab should be biological drug of choice in settings where patients with RA due to ineffectiveness or intolerance of MTX . In patients with RA, tocilizumab has shown better outcomes in functional as well as in structural changes, compared to monotherapy with TNF inhibitors or monotherapy with MTX (90-92).

Review of the cost effectiveness analyses of different therapeutic strategies in RA

Due to their high costs, prescription of biological drugs is limited with special set of demands and only in patients who previously failed with two drugs from DMARD-s including MTX (92, 94). The results of cost effectiveness studies which compare different TNF- inhibitors are mainly given by socio economic conditions and health policy of country where study was performed. Kobelt et al. have shown that infliximab were cost effective for rheumatoid arthritis in economic settings of Sweden and Great Britain, from societal perspective, since in the infliximab group direct and indirect costs were reduced and incremental cost effectiveness ratios (ICER) were close to threshold. The similar findings were in study conducted by Bansback et al which was performed in Sweden. TNF inhibitors have favorable cost effectiveness ratio in case where threshold was estimated from 50 000 to 100 000 €/QALY, and if threshold is 35000 €/QALY rituximab was found to be the most cost-effective alternative compared to other biologics among the patients with an insufficient response to TNF inhibitors (95). In our country, socio economic settings are different, the costs of the biological drugs are high as in other countries, while the costs of medical services are signifi-

cantly lower than in other countries, which leads that biological drugs, tocilizumab is not cost effective for treatment of RA compared do cDMARD-s (92, 93).

Targeted synthetic DMARD-s

The size of bDMARD-s (90000-150000 Dalton) provides that their mechanism of action is directed only at cytokines and molecules which are part of cell membrane. Orally available cDMARD-s have lower molecular weight and interfere with structure positioned in cytoplasm and directly regulate intracellular signal pathways. The process of phosporylation of kinase proteins especially of Janus kinase mediates processes of cell proliferation, differentiation and adhesion which are crucial for development of RA. Janus kinase (JAK) family involves homodimer or heterodimer of Jak1, Jak2, Jak3 and tyrosine kinase 2 (Tyk 2) (96).

Tofacitinib is the first orally approved targeted synthetic DMARD which inhibit family of Jak kinase. Tofacitinib in combination with MTX, in dose of 5 mg twice a day, has shown similar efficacy as biological therapy in patients with RA. In contrast to most biological drugs, tofacitinib was superior to MTX in patients with RA. Tofacitinib has been approved only in USA and other countries, but not yet in the European Union. The side effects of tofacitinib involve nasopharyngitis, elevation of transaminase and level of creatine, increase of total cholesterol, neutropenia and anemia (96-98).

The inhibition of pan-JAK is a promising new mechanism which induces production of palette of new orally drugs: baricitinib, decernotinib, peficitinib and filgotinib with expectations that they would be valuable therapy with cDMARD-s and bDMARD-s not only in RA, but also in other autoimmune disease (96).

CONCLUSIONS

The primary goal of therapy of RA is to achieve clinical remission and to prevent further structural and functional deterioration of affected joints. Early diagnosis and induction of DMARD-s are crucial for maintaining remission and prevention of complications of RA. The new concept in treatment of RA includes treat - to- target principal which provoke that treatment should last while remaining course of disease. The core of this principal encompasses selection of drug with high efficacy and low rate of hazards, dose reduction of drugs in a remission phase and even therapy discontinuation especially for bDMARD-s in patients with RA (46).

The selection of therapeutic strategies for RA due to all these reasons may be a challenge for clinical practitioners and should be based on clinical guidelines and recommendations which summarize global evidences of the highest level, but also on individual characteristics of patients (29).

The targeted synthetic DMARD-s are new therapeutic strategy for RA but its well defined position among other available therapeutic strategies should be investigated in efficacy aspects as well as in safety aspects (40).

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