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INVITED LECTURE

EARLY DIAGNOSIS AND THERAPY OF RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis is a chronic, progressive, systemic disease where most visible changes are in the joints that lead to the damage, which ultimately results in loss of function. In order to reduce damage to the joints it is necessary to diagnose early, before the appearance of erosion and to include adequate therapy. The problem is the lack of criteria for diagnosing the beginning of disease. Modified classification criteria of the American College of Rheumatology are not sensitive for the diagnosis at an early stage. It takes great knowledge and experience of rheumatologist to determine the existence of inflammatory arthritis, to exclude other possible arthritis, to determine the risk of developing persistent, erosive arthritis and that in time that is designated as a "window of opportunity" propose an optimal therapeutic strategy. EULAR has given recommendations for managing early rheumatoid arthritis.

Key words: *rheumatoid arthritis, early diagnosis, early therapy*

INTRODUCTION

The main clinical features of rheumatoid arthritis (RA) are a symmetrical, persistent and destructive polyarthritis with a positive finding of rheumatoid factor (RF) or anti-citrullinated antibodies (anti-CCP). In practice, often clinical features are unclear, and specific tests are lacking.

To start RA therapy on time and to prevent destructive changes on joints, it is necessary to set an early diagnosis, which is often a problem. Early diagnosis of RA is required for early treatment, before the occurrence of erosion, because it is rarely noted that erosion will disappear once it appeared, so that early treatment should become a major task. Bone erosion is occurring in a period of 6 months to 2 years from the beginning of disease.[1,2] It was found that after 6 months it occurs in 40% of patients, and after 2 years about 75% of patients have bone erosion.[3]

To set the early diagnosis there are number of problems, because there is no pathogonomic nor clinical or laboratory and radiological findings, and even that would enable to set a correct diagnosis.

The first step of early diagnosis is recognition of presence of inflammatory arthritis. The next step is the exclusion of other arthritis such as systemic lupus, psoriatic arthritis and other seronegative sponyloarthropathy. In the end, you need to determine the risk of developing persistent, erosive, irreversible arthritis and to determine the optimal therapeutic strategy.[4,5] There are two dangers, one is to diagnose RA, even when it is not, and to begin unnecessarily aggressive therapy and the other is hesitation and late treatment which falls into the risk of developing erosion and irreversible changes. On the erosive joint disease indicate clinical indicators (number of swollen joints), and laboratory findings (erythrocyte sedimentation accelerated-SE, high CRP, high RF, anti-CCP). Rheumatologist now generally agree to include modified drugs (DMARD) before erosion occur. [6,7]

If the patient meets the criteria of the American College of Rheumatology (ACR)[8] for the diagnosis of RA, it can no longer be spoken of early RA, because among the criteria are characteristic radiological changes,

rheumatoid nodules and morning stiffness over 1 hour. If ACR criteria are applied by an early RA than their sensitivities are 40-60%.[9] For the early diagnosis of RA, extensive knowledge is necessary of an experienced clinicians in taking data, for example morning stiffness is difficult to separate from pain, so it is difficult to determine its duration, especially in the beginning of the disease. Also information about the length of arthritis for patients is sometimes difficult to determine. There is a wrong assessment of inexperienced clinicians about the presence of swelling, particularly in some joints (elbows, foot joints, sometimes MTP, and MCP) on which the patients indicate that they are very painful.

To distinguish persistent arthritis from arthritis of the limited duration the test cross-hand grip can be used that is highly specific (84%) but it is poorly sensitive (48%). Among the clinical findings, which are most specific, is subcutaneous knots (99%) but poorly sensitive (2%) and has no diagnostic value for diagnosis of early RA. Patients who meet the ACR criteria for RA have a 50% chance to enter the remission after single dose of corticosteroid therapy if their disease is lasting less than 12 weeks.[10,11] This suggests that patients with arthritis duration shorter than 12 weeks have unstable arthritis, or very early stage of RA -very early RA (VERA) and can be completely healed. Those with arthritis over 12 weeks have small possibility of remission and this is confirmed RA where therapy should begin immediately.[12]

SEROLOGICAL MARKERS

Laboratory indicators in the early stages of RA are important, and in a large percentage, serological markers RF and anti-CCP are present. The problem is the phenomenon of early arthritis without these laboratory signs, because from it other arthritis can be developed or may spontaneously disappear. Great importance have anti-CCP, which have highly specific, which in early RA is 96%, while the sensitivity is 48%.[13] Other antibodies are not so specific. Their significance is that it may occur several years before the first symptoms, so other than diagnostic they have predictive value, and point to the poor prognosis, i.e. severe form of the disease. In cases of unexplained arthritis, by anti-CCP finding there is 70% probability that it will be RA.[14] They are to be determined in all patients with early arthritis.

RF is used a long time for the diagnosis of RA, although it is in healthy people as well, so finding RF, without sign of disease does not indicate the RA. If arthritis is present, then finding RF refers to the RA, because it is found in 70-80% of patients with RA and in 50-60% of patients with early RA. Higher titers of RF speak more severe form of disease and worse prognosis. A positive finding of anti-CCP and RF has a specificity of 98%, and sensitivity of 39%.

METHODS OF VISUALIZATION IN EARLY RHEUMATOID ARTHRITIS

Although the radiography of hands and feet is bound for the diagnosis of RA, it is not useful for diagnosis of early RA, because the erosion is not seen at the beginning of the disease. There are different opinions about what creates the intensity of radiological changes in the joints of RA. Anatomical damage to the joints is mostly generated in the first 5 years of disease, less in the next 5 years, and significantly less after 10. Separate analysis of six studies is made and it found that 70% of all patients develop erosive changes in the first or second year of disease.[15] There are different findings, showing prospective study of 256 patients with RA that was conducted in the period of 19 years and found that disease progression is going constantly, linear.[16] The problem is that these early changes in the structure of the joints can not be registered by radiography.

The highest value in the early stages has magnetic resonance imaging (MRI). MRI may also before the appearance of radiographic changes find signs of inflammatory process on joint structures, edema, effusion in the joint, a small erosion in the bones, cartilage damage, inflammation of the tibial tuberosity and the initial sinovitis.[17] It is not used routinely because of the very high cost of examination, but is indicated in cases of doubt, and can not otherwise prove RA. Scintigraphy can also detect inflammation in the joint before radiography changes. Other visualization method in the early stages is ultrasound and it is useful for diagnosis of sub clinical synovitis and computer tomography. Changes that are detected with MRI or ultrasonography have not yet found a place among the diagnostic criteria for RA.

THERAPY OF RHEUMATOID ARTHRITIS AT AN EARLY STAGE

Beside for a need for early diagnosis of RA there is a need for prognosis of the course if disease, which determines the type of therapy. The poor prognosis in RA indicates grasping with disease more joints in a short time, positive RF, high SE, CRP and the presence of rheumatoid knots.[18,19] It seems that the most consistent prognostic factor is positive RF, as for the progression of joint damage as for functional disability.[20]

In RA an important fact for therapy is the presence of constant inflammation, because damage to joints is

higher if inflammation takes longer, which indicates that the duration of inflammation is more important than the intensity of inflammation. Calming inflammation decreases joint damage. Time from occurrence of inflammation to the appearance of first damage is 'window of opportunity'; and it is a period when more can be achieved by aggressive treatment to slow or stop the progression of disease.[21] The reason for this is that pathop-hysiological changes in early RA may be reversible, if adequate therapy is on time.

European League Against Rheumatism (EULAR) has made a recommendation for managing early RA which was made by 14 rheumatologist from 10 European countries that have spent more time involved in research on early arthritis.[4] From it came the following 12 recommendations:

1. Arthritis is characterized by the presence of joint swelling, associated with pain and stiffness. A patient with arthritis of more than one joint should be examined by the rheumatologist ideally within 6 weeks after symptoms appear.
2. Clinical examination is the method of choice for the detection of synovitis. In suspicious cases ultrasound or MRI can be helpful.
3. Exclusion of other diseases is performed with careful anamnesis, clinical examination and laboratory tests: complete blood test, urine analysis, transaminases, and antinuclear antibodies.
4. In all patients where early arthritis is seen by rheumatologist following factors predict persistent and erosive disease: the number of painful and swollen joints, rapid SE, high CRP, RF, anti-CCP and radiographic erosion.
5. Patients with risk of developing persistent or erosive arthritis should start with a disease modified anti-rheumatic drugs (DMARD), as soon as possible even if it does not meet the established classification criteria for inflammatory rheumatic disease.
6. It is important to inform patients concerning the disease, treatment of disease and the results that will be given through the process of education.
7. Nonsteroidal anti-inflammatory drugs (NSAID) as symptomatic therapy in early arthritis should be given after evaluation of the risk of gastrointestinal, renal and cardiovascular system.
8. Systemic therapy with glucocorticoid drugs reduce pain and swelling and should be considered in addition to DMARD therapy. Intra articular injection of glucocorticoid drugs helps local symptoms of inflammation.
9. Among DMARD metotrexat should be used first by patients who have a risk of developing persistent disease. Leflunomid and some Sulfasalazin can be considered as a good alternative, if for some reason the patient can not take Metotrexat.
10. The main goal of DMARD treatment is to achieve remission. Regular monitoring of disease activity and adverse events should be conducted by the decision of choice and changes in treatment strategy (including biological therapy).
11. Non-pharmacological interventions like physical and occupational therapy are included as an addition to pharmacological treatment since the beginning of disease.
12. Monitoring of disease activity should include the number of painful and swollen joints, patient and doctors' assessment, SE and CRP. Arthritis activity should be evaluated at intervals of one to three months until a longer remission. Structural damage should be assessed by radiography of hands and feet every 6-12 months for the first few years. Functional assessment (e.g. HAQ) can be used to complete the monitoring of disease activity and structural damage.

CONCLUSION

Solving the problem of RA means resolving deformation on the joints, destructions, difficult and painful mobility and functional disability. Making the diagnosis according to ACR criteria means delay in diagnosis. It is necessary to establish criteria for early diagnosis, before the occurrence of erosion, start early in therapy, so that it can be expected not to have the destruction of the joints, prevents progression, and there is no functional disability. Since we still have no findings that are pathognomonic for RA, we can not determine the criteria for early RA. It remains to provide even greater importance of knowledge and experience of rheumatologist and his ability to diagnose according to current diagnostic procedures is of utmost importance for optimal therapeutic strategy.

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