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IMPORTANCE OF MONITORING MATRIX METALLOPROTEINASE-3 LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS

Iroda X. Xadjimatova [1], Ma`rif Sh. Karimov [2], Dilorom A. Abzalova [3]

1 Basic doctoral student of the Department of Propaedeutics of Internal Medicine, Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: xajimatova92@mail.ru

2 Professor, Doctor of Medical Sciences, Head of the Department of Propaedeutics of Internal Medicine Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: karimov.marif58@mail.ru

3 Assistent of the Department of Propaedeutics of Internal Medicine, Tashkent Medical Academy, Tashkent, Uzbekistan
E-mail: abzalova1955@gmail.com

ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation and gradually progressive bone destruction. Matrix metalloproteinases (MMPs), a family of zinc-containing enzymes, have been found to play an important role in the degradation and remodeling of the extracellular matrix (ECM).

Matrix metalloproteinases (MMPs) are involved in cell proliferation, migration, inflammation, and cell metabolism. More and more people are paying attention to their function in inflammatory and immune diseases.

Key words: rheumatoid arthritis, matrix metalloproteinase-3, DAS 28, SDAI, CDAI.

INTRODUCTION

In RA, the main role is played by 3 types of MMP: collagenases, stromelysins and gelatinases. The main role is assigned to MMP-3 (stromelysin -1), MMP-1 (fibroblast collagenase), MMP-8 (neutrophil collagenase), MMP-9 (gelatinase-2) and MMP-13 (collagenase-3). Among them, the leading role in the destruction of articular cartilage belongs to MMP-3 [9-12]. It is produced by synovial cells [12], is found in synovial tissues in the form of a proenzyme and is activated by plasmin [13], after which it itself activates proenzymes of other MMPs [12,13].

In RA, the level of MMP-3 in the serum increases 7-8 times. Thus, Y. Ichikawa et al. [3], studying the concentration of MMP-3 in 60 patients with RA and 21 with systemic lupus erythematosus (SLE), noted a significant increase in the level of MMP-3 (436.8 ± 474.2 ng/m l) in the study group compared to the control (43.9 ± 15.2 ng/m l, p <0.0001). The enzyme matrix metalloproteinase-3 (MMP-3), also known as stromelysin-1, is encoded in humans by the MMP-3 gene, which is part of the MMP gene cluster located on chromosome 11q22.3. MMP family proteins are involved in the degradation of extracellular matrix proteins during tissue remodeling in normal physiological processes such as embryonic development and reproduction, as well as in disease processes such as arthritis and tumor metastasis. Most MMPs are secreted as inactive pre-proteins that are activated by cleavage by extracellular proteinases. MMP-3 is a proteinase synthesized and secreted by synovial fibroblasts and chondrocytes in joints. It is actively involved in joint destruction in patients with RA. The MMP-3 enzyme degrades collagen types II, III, IV, IX and X, proteoglycans, fibronectin, laminin and elastin. In addition, MMP-3 can also activate other MMPs such as MMP-1, MMP-7 and MMP-9, making MMP-3 a critical factor in connective tissue remodeling [12, 13]. MMP-3 and plasmin can affect inflamed synovial tissues and promote joint destruction [3]. Moreover, the higher the level of serum MMP-3, the greater the joint destruction, which was confirmed in the work of I. Chetverikov et al. [14], who examined RA patients with moderate and severe joint destruction. It turned out that the latter had a significantly higher level of MMP-3. This allowed us to conclude that serum MMP-3 is a prognostic factor for joint damage in the early stages of the disease. The implementation of MMP action is regulated at various stages, including gene activation, transcription, translation, and secretion of the enzyme with activation of its proenzyme. Once MMPs are produced and activated, their action and subsequent inactivation is controlled by tissue inhibitors of metalloproteinases (TIMPs) produced in the inflamed synovial tissue. MMPs are produced in response to the proinflammatory cytokines TNF-a and IL-1 [15] and are found in excess in the inflamed joint [1]. Degradation of articular cartilage is one of the early features of diseases associated with increased activity of proteolytic systems [11]. Dysregulation of MMPs is manifested in RA, osteoarthritis (OA) and cancer [7, 12]. Progressive destruction of the extracellular matrix, including articular cartilage, bone, ligaments and tendons, is the main feature of arthritis, leading to impairment of the patient's functional capacity [10]. MMPs are involved in RA-associated bone destruction mainly through three mechanisms:

1) Adhesion to chondrocytes leading to collagen degradation and subsequent cartilage damage;

2) Regulation of inflammatory cytokines and chemokines leading to homeostasis imbalance in the affected joint and activation of inflammatory signaling pathways that promote osteoclast differentiation and bone resorption;

3) Stimulation of cell migration and invasive angiogenesis, initiating signals of osteoblast-osteoclast balance and accelerating bone destruction.

The aim of the study was to establish the value of matrix metalloproteinase-3 level in patients with rheumatoid arthritis.

Research materials and methods. We examined 45 patients with RA undergoing inpatient treatment in the rheumatology department of the multidisciplinary clinic of the Tashkent Medical Academy for the period from 2022 to 2024. The following indicators served as criteria for patient selection: persons of both sexes aged 30-75 years with RA of varying activity. General examination of patients was conducted according to the plan adopted in the clinic. The average age of the examined patients was 46.5 ± 4.5 years. When making a diagnosis, the following criteria were taken into account:

- articular syndrome occurring in the form of mono or oligo arthritis, unilateral or bilateral sacroiliitis;
- history of clinical complaints about the general condition of the liver;
- age and duration of RA;
- presence of extra-articular manifestations of RA.

The course of RA was divided into acute (duration of the disease up to 6 months), protracted (from 6 months to a year) and chronic (more than 1 year).

RA activity was determined by the intensity of pain, the presence of effusion in the joint cavity, the presence of joint dysfunction, an increase in ESR and CRP and ACPA. The stage of synovitis was determined using X-ray examination. The duration of the anamnesis of the examined patients ranged from 6 months to 8 years. Depending on the duration of the disease, RA patients were divided into patients with an anamnesis duration of up to 6 months (12% of patients), up to 1 year (14%), from one year to 5 years (37%) and more than 5 years (37%). The largest number of patients had an anamnesis duration of 1 to 10 years. A general assessment of health status was carried out using a visual analogue scale (VAS), on which the patient marks a score from one to ten, corresponding to the severity of pain and general condition. The results of the analogue scale were interpreted as follows: no pain – 0 points; mild pain – 1-2 points; moderate pain – 2-4 points; severe pain – 4-6 points; 6-8 points – severe pain; and 9-10 points – unbearable pain.

All patients underwent the following laboratory and instrumental studies: complete blood count, biochemical blood test, immunofluorescence analysis of MMP-3, IgM.

SPSS for Windows, 22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical processing of the obtained data. Quantitative variables were compared using the Student t test and the Mann-Whitney test, and qualitative variables were compared using Fisher's exact method. Survival was analyzed using the Kaplan-Meier method. The difference was considered statistically significant at $p < 0.05$.

The results of the study. In the group as a whole, the MMP-3 level significantly decreased after 12 and 24 weeks of therapy by 49.3 and 93% from the initial level and amounted to 23.7 (1.5-44.5) ng/ml and 3.25 (0.025-29.0) ng/ml, respectively, $p<0.05$. Against the background of MT monotherapy, this indicator after 12 and 24 weeks decreased by 49.3 and 99.7% from the initial level and amounted to 23.7 (1.5-44.5) ng/ml and 0.025 (0.025-29.0) ng/ml, $p<0.05$. Against the background of combination therapy, the level of MMP-3 decreased by 45.9 and 88.4% (31.7 (16.3-72.0) ng/ml and 7.0 (0.03-29.0) ng/ml, respectively, $p<0.05$) (Figure 1).

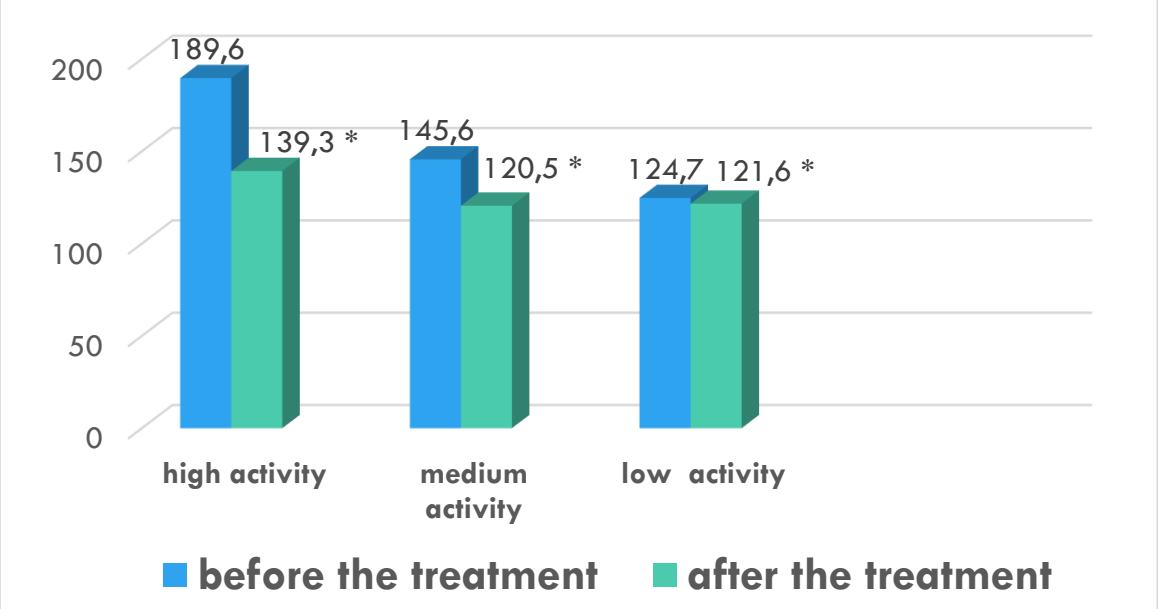

Figure 1. Dynamics of MMP-3 levels before and after combination therapy (* p <0.05 compared to baseline).

We also assessed the initial disease activity and MMP-3 levels in patient groups depending on the effect of MT by the 3rd month of treatment; for this, all patients were divided into 2 groups. Among patients with a good MT effect (n=16), lower inflammatory activity (DAS 28 4.4 (4.4-5.7), SDAI 24.1 (16.9-35.7), CDAI 20.7 (15.8-30.0)) and MMP-3 levels (10.6 (0.03-38.1) ng/ml) were initially recorded compared to patients receiving combination therapy (n=29) (6.05 (5.3-

6.7), 40.7 (26.7-48.2), 35.8 (23.5-42.8), and 58.8 (27.0-106.3) ng/ml, respectively, p<0.05 between groups in all cases) (Table 1).

Table 1. Initial clinical and laboratory activity of the disease in patient groups depending on the effect of MT by the 5th week of therapy, Me (IR)

Indicator	MT monotherapy	Combination therapy
DAS28, points	4,9 (4,4-5,7)	6,05 (5,3-6,7)
SDAI, points	24,1 (16,9-35,7)	40,7 (26,7-48,2)
CDAI, points	20,7 (15,8-30)	35,8 (23,5-42,8)
ММП-3, ng/ml	10,6 (0,03-38,1)	58,8 (27,0-106,3)

Note: p<0.05 between groups in all cases.

We analyzed the information content of MMP-3 level determination before and 5 weeks after the start of MT treatment to predict drug efficacy after 3 months.

According to the ROC analysis, it was found that the initial level of MMP-3 over 54.6 ng/ml, as well as the persistent increase in the level of this indicator over 25.1 ng/ml after 5 weeks, is associated with the absence of the effect of MT after 3 months and the need to prescribe combination therapy (AUC=0.78, 95% CI 0.63-0.93 and AUC=0.76, 95% CI 0.54-0.86, respectively) (Figure 2).

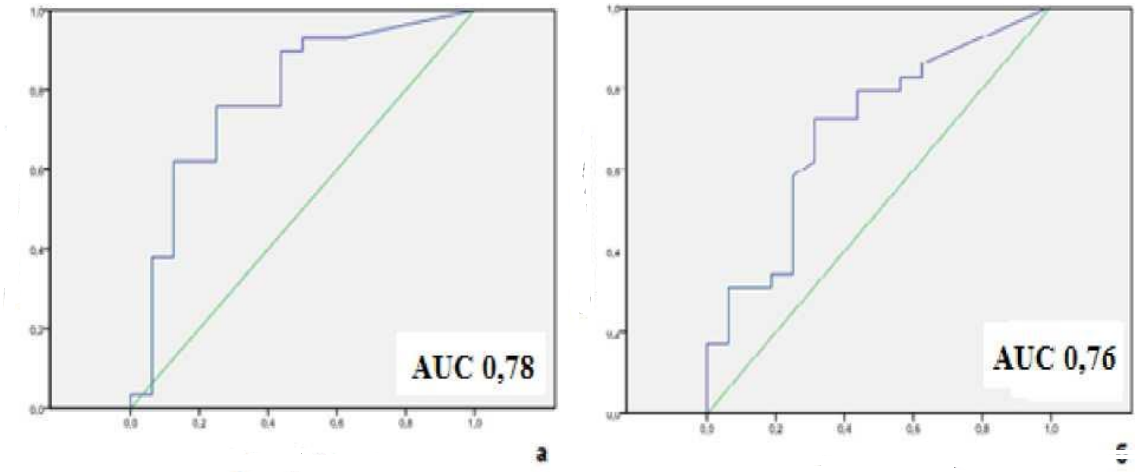

Figure 2. ROC curve reflecting the information content of determining the basal level of MMP-3 (a), as well as the level of MMP-3 after 5 weeks of MT therapy (b) for predicting the effectiveness of the drug after 3 months of treatment.

The results of the study indicate the important role of MMP-3 for assessing disease activity, monitoring therapy effectiveness, and predicting treatment outcomes for early RA. The serum MMP-3 content both with MT monotherapy and with the use of a combination of MT and GIBP decreased after 4 weeks of treatment, reaching 49.3 and 45.9% of the baseline level, respectively.

Conclusion. Determination of basal MMP-3 levels may be useful for predicting the clinical efficacy of DMARD and GIBP therapy in RA. In the present study, MT was more effective in patients with baseline MMP-3 levels less than 54.6 ng/ml and with a decrease to less than 25.1 ng/ml after 5 weeks of treatment.

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