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Short Article

Rheumatoid arthritis – usage of biomarkers in disease' prognosing, diagnosing and monitoring

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic inflammatory joint disease which has a significant, negative influence of patients' quality of daily life. In routine clinical practice there is a usage of classic biomarkers, such as rheumatoid factor (RF) and anti-citrullinated antibodies (anti-CCP), as well as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in detecting onset or exacerbation of the disease and in monitoring its course.

Aim: The study presents other markers with higher sensitivity and specificity which will let doctors identify even smoldering systemic inflammation and introduce appropriate treatment to prevent serious consequences of RA, including joints' erosion and disability.

Methodology: This review was conducted using a systematic approach to identify and analyze relevant scientific literature on the potential biomarkers of RA activity and progression and to indicate their practical clinical implications. We searched PubMed and Google Scholar databases. Articles were searched using following words : "Rheumatoid

arthritis", "biomarkers", " inflammatory", "progression"," treatment".

Summary: In a group of promising markers there are: calprotectin (S100A8/S100A9), 14-3-3η, antibodies against carbamylated proteins (anti-CarP), metalloproteinase 3 (MMP-3), other MMPs and cytokines (IL-1, IL-6, TNF-α).

Keywords: Rheumatoid arthritis, biomarkers, inflammatory, progression, treatment

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with a heterogeneous course, leading to cartilage damage, bone erosion, joint deformity, and reduced quality of life[1,2]. Despite significant advances in treatment (including the widespread use of sDMARDs and bDMARDs), there is still a need in everyday practice for earlier diagnosis of inflammatory changes and tissue damage, monitoring of disease activity in a more sensitive way than just clinical symptoms and standard acute phase indicators, identification of patients at high risk of radiological progression and disability, selection of optimal therapy (personalization), and prediction of response to treatment[3].

In this context, biomarkers-molecular, serological, cellular - and their integration with imaging are a promising direction. The aim of this article is to present the current state of knowledge on biomarkers of RA activity and progression and to indicate their practical clinical implications.

Results

Classic markers - still the starting point

In routine clinical practice, the basic markers are: Rheumatoid factor (RF) – antibodies directed against Fc immunoglobulins. The presence of RF is associated with greater disease activity and

a poorer prognosis[4]. Anti-citrullinated antibodies (ACPA, e.g., anti-CCP) - highly specific for RA, often present at an early stage, predictive of erosion. Acute phase markers: CRP and ESR- reflect systemic inflammation; are included in standard activity monitoring (e.g., in DAS28-CRP)[5].

These markers continue to play a key role in diagnosis, classification, and therapy monitoring. However, their limitations are becoming increasingly apparent: for example, CRP/ESR may be normal despite active joint inflammation (especially under the influence of IL-6 blocking drugs). Therefore, there is a need for more sensitive, specific, or complementary biomarkers[6].

New and promising biomarkers

Calprotectin (S100A8/S100A9)

Mechanism: a heterodimer of S100A8 and S100A9 proteins (also known as MRP8/14) released from activated neutrophils and macrophages, present in synovial fluid and serum. A systematic review showed that calprotectin levels are elevated in RA, correlate with disease activity, and predict erosion[7]. A study in patients treated with IL-6 antagonists or JAK inhibitors showed that plasma calprotectin concentrations were significantly higher in those with US-detected synovitis than in those without; AUC ~0.795 (95% CI: 0.687-0.904) - better than for hs-CRP or ESR[8]. Calprotectin may be useful as an indicator of active joint inflammation (including subclinical).

Limitations include the lack of universally established reference thresholds, the influence of treatment and other inflammatory factors, and the fact that it is not yet standard in most clinical laboratories. It can be used as a supplement to APR in monitoring disease activity, especially when CRP/ESR do not reflect the actual state of inflammation[9,10].

14-3-3η(eta)

Protein isoform 14-3-3η (part of the 14-3-3 family) mainly found outside cells in the joints of patients with RA; activates pro-inflammatory pathways and metalloproteinases[11]. A study in Clinical & Experimental Rheumatology showed that using an ELISA test (cut-off 0.19 ng/ml), sensitivity was ~63.6% and specificity was ~92.6% for the diagnosis of RA. Adding 14-3-3η to ACPA increased the identification of patients with early RA from 59% to ~72%[12].

Another study showed that 14-3-3η significantly correlates with radiological damage in RA (original Egyptian study: cut-off 31.05 ng/ml, sensitivity 86.7%, specificity 84.0% when combined with Larsen score and CIMT)[13].
In summary, 14-3-3η may support diagnosis, especially in seronegative patients (RF- and ACPA-), and also serve as an indicator of the risk of joint damage progression. Less multicenter data than for ACPA/RF; standardization of tests and interpretation thresholds is needed. It is worth considering as an addition to the diagnostic panel in unclear or seronegative cases. It may help identify patients at higher risk of progression.

Anti-CarP (antibodies against carbamylated proteins)

Autoantibodies against carbamylated proteins (modification independent of arginine deimination as in ACPA). More and more studies in the literature indicate that anti-CarP positivity is associated with faster erosive progression even in ACPA-negative patients. A potential prognostic biomarker, especially in ACPA-negative cases.
Limitations include: reduced availability of the test, diversity of measurement methods, and less long-term data.
May be considered in a prognostic panel for early patients or those suspected of having an aggressive course[14,15,16,17,18].

Markers of tissue degradation / enzymatic / imaging

Metalloproteinase 3 (MMP-3), other MMPs, cytokines (IL-6, IL-1, TNF-α), chemokines - are associated with inflammatory activity and tissue damage[19,20,21]. Imaging: US (with power Doppler) and MRI remain the gold standard for detecting joint inflammation and erosion. In many studies, the correlation of biomarkers with US results has been used as the "gold" standard. Imaging and markers of degradation often provide the best prognostic guidance, but they are less accessible/more expensive than serological tests. Limitations include the cost and availability of US/MRI in routine practice, high variability in cytokine levels, and interpretation in the context of treatment. In cases of high risk of progression or unclear inflammatory activity, imaging + degradation markers should be considered as a supplement[22,23,24].

Discussion

Clinical aspects

In diagnostics, early diagnosis of RA is still based on RF, ACPA, CRP/ESR, clinical presentation, and imaging. When RF and ACPA are negative and clinical suspicion is high, it is worth considering additional tests: 14-3-3η, anti-CarP. These tests do not replace clinical examination, but they can increase the certainty of diagnosis and identify high-risk patients.
CRP and ESR are still commonly used to monitor disease progression, but their limitations should be kept in mind (e.g., under the influence of IL-6 blocking drugs, when CRP may be underestimated). Calprotectin may be a valuable marker for monitoring joint activity, including subclinical synovial activity, especially when ultrasound may not be available or a biomarker for regular measurement is desired. Clinical decisions to modify therapy should take into account the clinical picture, laboratory results, and, if possible, imaging[25,26,27].

Patients with ACPA, high RF titers, 14-3-3η positivity, and anti-CarP represent a group at increased risk of joint damage progression-for them, modification of the therapeutic strategy (e.g., earlier initiation of bDMARD) may be justified. The idea of personalizing treatment should be emphasized: choosing a treatment strategy, intensification, more frequent monitoring, or the use of advanced imaging in “high-risk” patients. Multi-marker models (e.g., MBDA-Multi-Biomarker Disease Activity) and machine learning algorithms offer potential, although they require further validation in clinical practice[28,29,30,31].

Conclusion

Biomarkers remain a key element of modern RA diagnosis and monitoring. Classic indicators (RF, ACPA, CRP, ESR) remain essential, but their sensitivity in assessing disease activity is limited, especially in the era of modern biological therapies. New biomarkers, such as calprotectin, 14-3-3η, and anti-CarP antibodies, provide valuable prognostic information.
Calprotectin reflects subclinical inflammation better than CRP, 14-3-3η can aid in the diagnosis

of seronegative forms of RA, and the presence of anti-CarP is associated with a more destructive course of the disease. An integrated approach combining biomarkers with imaging (US, MRI) increases the precision of activity and progression risk assessment.
This approach enables earlier therapeutic response and more accurate monitoring of remission.

Disclosure

Author's contribution

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Conflict of interest

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