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A Blood Biomarker Panel Recommended for Personalized Prediction, Prognosis and Prevention of Rheumatoid Arthritis

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ABSTRACT

Keywords: Rheumatoid Arthritis; Inflammation; Synovial Tissue; PPPM Principles; Early Diagnosis; Biomarker Panel; Prognostic Factors; Monitoring Disease Activity; Predictive Biomarkers; Disease Management

Abbreviations: RA: Rheumatoid Arthritis; CRP: C Reactive Protein; ESR: Erythrocyte Sedimentation Rate Parameter; PPPM: Preventive And Personalised Medicine; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; ACPA: Anti-Citrullinated Peptide Antibodies; Anti-MCV: Anti-Mutated Citrullinated Vimentin; TNF-α: Tumour Necrosis Factor α

Introduction

Rheumatoid arthritis (RA) is the most common chronic autoimmune joint disease affecting synovial tissue in multiple joints. The course of RA can be very heterogeneous and patients with the same diagnosis can present with different symptoms and outcomes as well as the possible development of irreversible joint damage leading to loss of function. Evidence suggests that RA develops in 3 phases: an asymptomatic period of genetic risk, a pre-clinical period in which RA-related antibodies can be detected, and a clinical phase with the clinical symptoms of inflammatory arthritis. Early detection of RA and the availability of biologic agents have markedly improved outcomes in these patients [1]. At present, composite indices (mostly DAS28, Disease Activity Index) are used to monitor the activity of the disease. They include clinical parameters (tender and swollen joints), and two laboratory parameters of inflammation: C reactive protein (CRP) and erythrocyte sedimentation rate parameter (ESR). The disadvantage of these scores is.

The degree of subjectivity of some of the criteria. Moreover, a significant proportion of the patients with negative inflammatory tests still have active disease.

Rheumatoid Arthritis and PPPM

RA is a typical example of a disease that requires new ways of succeeding in early diagnosis and subsequent treatment. The principles of predictive, preventive, and personalised medicine (PPPM) [2] and their appropriate application can be a good starting point for chang-

ing the general approach to RA management [3]. There is a clear need to find efficient diagnostic and prognostic biomarkers of this disease to identify patients with rapidly progressive destructive arthritis and rapid functional decline [4]. PPPM enables the prediction of individual predisposition to the disease, can help with targeted preventive measures, and create personalised treatment algorithms tailored to the individual. The above mentioned PPPM rules contribute to the cost-effective management of the disease [5]. PPPM principles are, at present, slowly entering clinical practice. This effort is most visible in the search for new biomarkers, starting with genetic biomarkers and followed by single blood biomarkers for the multi-omics approach [6].

The Role of Biomarkers in RA Diagnostics and Treatment

Progress in understanding the pathogenesis of RA has led to an increase in interest in studying the biomarkers involved in different stages of the disease. The use of biomarkers began many years ago in another field of medicine; namely oncology [7]. Together with the rules of PPPM, we can learn from the use of biomarkers and expand this into other fields of medicine [8]. There are several key stages of RA, and their proper management may influence its further prognosis, progression of disease, and its management (Table 1). Early diagnosis and immediate, effective therapy are crucial for the prevention of joint deterioration, functional disability, and unfavourable disease outcome. The 2010 RA classification criteria from the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) consists of symptoms and laboratory findings within 4 domains (total score 10 points). 40% of this total possible score relies on laboratory tests. Up to 3 points are generated by the presence of rheumatoid factor (RF) and/or anti-citrullinated peptide antibodies (ACPA). Equal weight is given to RA and ACPA. Amongst ACPAs, anti-CCP, the anti-cyclic citrullinated peptide assay, has a superior diagnostic and prognostic value. The sensitivity of the anti-CCP assay in RA is 60–80%, with a very high specificity of 95–99% [1]. The assay has a high significant predictive value and the autoantibody can be found early, even in the preclinical phase of RA. Besides these, some new diagnostic biomarkers that can aid the early diagnosis of RA have been identified.

Table 1: Biomarkers in the PPPM approach.

Early diagnosis	Starting treatment in the early stages prevents osteoarticular destruction
Prognostic factors	Identifying patients at high risk of an aggressive form of RA
Monitoring disease activity	Evaluating treatment efficacy
Predictive factors for therapy	Biomarkers predictive of the response to treatment

Anti-Mutated Citrullinated Vimentin (anti-MCV)

Vimentin is a protein that can be citrullinated, a reaction mediated by peptidyl arginine deiminase. Anti-mutated citrullinated vimentin (anti-MCV) is a key autoantibody of the ACPA family, where vimentin is secreted and citrullinated by macrophages in response to apoptosis, or pro-inflammatory cytokines such as tumour necrosis factor α (TNF-α). A meta-analysis from 2010 that included 14 studies in which anti MCV and anti-CCP were tested, concluded that there is not a substantial difference between the two tests. Thus, determination of anti-MCV seems to be useful as a line 2 test in patients suspected of having RA but is negative for both RF and anti-CCP. Anti-MCV antibody levels were measured at baseline, and at one and two-year follow up in 162 patients with early arthritis. It was found that anti-MCV positive patients had a higher structural progression and higher ESR and CRP levels than did anti-MCV negative patients at all chronological points [9].

14-3-3η Protein

The 14-3-3 family of proteins is a family of chaperone proteins. They play a role in several inflammatory processes and consist of 7 isoforms. Studies looking at the 14-3-3 levels have in fact found that they correlate with the levels of matrix metalloproteinases and other markers that break down cartilage and bone. It appears that the combination of 14-3-3η protein, RF and anti-CCP will help to increase the sensitivity and specificity for patients with early active disease, help to stratify RA patients, and allow us to tailor treatments for patients in early stages. In a study conducted on 619 subjects, 14-3-3η protein sensitivity and specificity for RA was 77% and 93% respectively. In the early stages of the disease, the determination of protein 14-3-3η along with RF and anti-CCP increases the diagnostic rate from 72% (RF + anti-CCP) to 78% (RF + anti-CCP + 14-3-3 η). It may predict both clinical and radiographic progression, as well as treatment response. Lower 14-3-3η levels were found in patients achieving remission during biologic therapy with anti-IL 6 monoclonal antibody (tocilizumab). Post-treatment 14-3-3η expression is significantly different between stages [10].

The Multi-Biomarker Disease Activity Index (MBDA index)

Commercially known as the Vectra DA, it was developed and validated in more than 1800 unique patients and biospecimens over quite several years. During development of the MBDA score, 96 candidate biomarkers were reduced to 12 (CRP, leptin, resistin, serum amyloid A, IL-6, TNF-RI, VEGF-A, MMP-1, YKL-40, MMP-3, EGF, VCAM-1), that run as a single test and result in a score of 0-100. Depending on the values of this score, the disease activity can be classified into mild (1-28), moderate (29-43) or severe (>44). The score has been examined in different cohorts (the SWEFOT study, the BRASS registry, and the Leiden Early Arthritis Cohort) [11]. The MBDA score is a very good determinant of subclinical disease activity and progressive disease with structural progression. In addition, the MBDA score may be able to direct which patients should receive more aggressive or more expensive therapy, and which patients may do well with conventional

therapy.

Calprotectin

Calprotectin (also known as the S100 protein) might be a valuable marker of RA disease activity. Calprotectin differs from other laboratory markers in its local production from activated synovial cells and release from inflamed synovium. As a consequence, calprotectin directly reflects the number of activated macrophages and the extent of inflammation. Calprotectin might be superior to CRP for the detection of patients in clinical remission with subclinical disease activity. Several authors have reported increased calprotectin serum levels in RA patients, its association with disease activity, its dynamic decrease after initiation of effective treatment and its role in predicting response to treatment [12,13].

Conclusions and Expert Recommendations

The goal of current and future biomarker use in rheumatic diseases is to enable early detection, effective monitoring and treatment regimens that are tailored to each patient's needs.

- We identified the following four parameters with the highest potential to establish a useful place in RA diagnostics and disease activity assessment, as well as in the prognosis of disease course and treatment response: anti MCV, 14-3-3η protein, MBDA score and calprotectin.
- The MBDA index is a panel of biomarkers that correlate with disease activity both clinically and radiographically.
- Serum biomarkers had stronger observed associations with joint damage than did clinical assessment.
- A multi-biomarker score for structural damage has the potential to aid assessment of joint damage risk, identify patients who most need joint sparing therapy and track disease changes in response to therapy.
- PPPM principles are currently making a slow entry into clinical practice.
- New biomarkers, together with suitably applied PPPM rules, help in the cost-effective management of the diseases, including RA.

Compliance with the Ethical Standards

Competing Interest

The authors declare that they have no competing interests.

Ethical Approval

Not applicable.

References

1. Nakken B (2017) Biomarkers for rheumatoid arthritis: From molecular processes to diagnostic applications-current concepts and future perspectives. Immunology Letters 189: 13-18.
2. Golubnitschaja O, Costigliola V, EPMA (2012) General report & recommendations in predictive, preventive, and personalised medicine 2012: white paper of the European Association for Predictive, Preventive and Personalised Medicine. EPMA J 3: 14.
3. Golubnitschaja O, Baban B, Boniolo G, Wang W, Bubnov R, et al. (2016) Medicine in the early twenty-first century: paradigm and anticipation-EPMA position paper 2016. EPMAJ 7: 23.
4. Gavrilă BI (2016) Biomarkers in Rheumatoid Arthritis, what is new? J Med Life 9(2): 144-148.
5. Lemke HU, Golubnitschaja O (2014) Towards personal health care with model-guided medicine: long-term PPPM-related strategies and realisation opportunities within 'Horizon 2020'. EPMAJ 5: 8.
6. Lu M, Zhan X (2018) The crucial role of multiomic approach in cancer research and clinically relevant outcomes. EPMA J 9: 77-102.
7. Hu R, Wang X, Zhan X (2013) Multi-parameter systematic strategies for predictive, preventive, and personalised medicine in cancer. EPMA J 4(1): 2.
8. Molacek J, Treska V, Zeithaml J, Hollan I, Topolcan O, et al. (2019) Blood biomarker panel recommended for personalized prediction, prognosis, and prevention of complications associated with abdominal aortic aneurysm. EPMA J 10: 125-135.
9. Ursum J (2008) Antibodies to mutated citrullinated vimentin and disease activity score in early arthritis: A cohort study. Arthritis Res Ther 10: R12.
10. Maksymowych WP (2014) Serum 143-3η is a novel marker that complements current serological measurements to enhance detection of patients with rheumatoid arthritis. J Rheumatol 41: 2104-2113.
11. Landewé R (2011) Barriers to effective disease activity monitoring in rheumatoid arthritis - clinical practice and implications for treat to-target guidelines. Eur Musculoskeletal Review 6: 88-93.
12. Hurnakova J, Hulejova H, Zavada J, Hanova P, Komarc M, et al. (2017) Relationship between serum calprotectin (S100A8/9) and clinical, laboratory and ultrasound parameters of disease activity in rheumatoid arthritis: A large cohort study. PLoS One 12: e0183420.
13. Cerezo L (2011) Decreases in serum levels of S100A8/9 (calprotectin) correlate with improvements in total swollen joint count in patients with recent-onset rheumatoid arthritis. Arthritis Res Ther 13: R122.

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