Review Article

The Role of Biomarkers in Diagnosis, Prognosis, Treatment, Determining Disease Activity in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory and complex autoimmune disease. It affects mainly small joints (of the hands and feet) and has many systemic manifestations.
The study of biomarkers in rheumatology is important to understand the mechanism involved in some rheumatic diseases. Discovering new biomarkers with key roles in various stages of the disease remains as an important issue in RA patients. Biomarkers are important for diagnosis and prognosis, target therapy, and guiding the clinical and response treatment of all phases of RA. Biomarkers improve diagnosis by closing the serological gap, providing prognostic information that allows disease activity and progression to be monitored. Biomarkers can be correlated with a risk of developing RA and can predict bone erosions and disease progression. Therefore, there is a need for a sensitive biomarker for early diagnosis of the disease. Some biomarkers are not specific (Rheumatoid Factor IgM) and some are not widely used due to technical problems (Antiprenuclear factor). On the other hand, anti-cyclic citrullinated peptide (anti-CCP) in the serum of patients are more specific for these patients.This move from traditional approaches to use more specific biomarkers for patient stratification and targeted treatment should greatly improve patient care and reduce medical costs.

Keywords: Rheumatoid arthritis, Biomarker, Diagnosis, Prognosis, disease activity

Introduction

Rheumatoid arthritis (RA) is an inflammatory, chronic and a complex multisystem autoimmune disease characterized by synovial inflammation and destruction of the joints. Although RA is generally a joint disease, there are extra-articular organ involvement, including the skin, eye, heart, lung, renal, nervous and gastrointestinal systems(1). It affects about 0.5% of the adult population in developed countries, 0.4% in Southeast Asia, and 0.37% in the Eastern Mediterranean(2, 3). In addition to reducing the life expectancy of patients, this disease has serious problems that make it impossible for 50% of patients to continue their occupational activity(4).

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In recent years, despite advances in controlling the disease, results show that only less than 50% of patients recover and because of the lack of a personalized and tailored approach to each patient, the results do not match the therapeutic goals(5, 6). The identification of biomarkers for diagnosis and prognosis of RA patients is essential, especially in people with the poor prognosis(7, 8). There are several biomarkers for investigation, but cellular events alter protein biomarkers, which reflect changes in cell signaling(9). The progression of the disease is accompanied by changes in the proteins, which are identified by proteomics to determine the progression and severity of the disease(10). A group of biomarkers changes after treatment that are appropriate for monitoring treatment responses(11). Biomarkers are involved in confirming, diagnosing and predicting outcomes or recommending specific therapies. At the present time, the diagnosis of patients with RA

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has been based on American college of rheumatology (ACR) criteria and sometimes the diagnosis may take a long time. Therefore, there is a need for a sensitive and specific biomarker for early diagnosis of the disease. Since the disease progression has a different pattern in patients, it would be more useful if biomarkers were related to the severity and activity of the disease and could predict disease progression. In this study we set out to determine diagnostic/prognostic value of different biomarkers for early treatment decision in RA patients.

Diagnostic biomarkers in Rheumatoid arthritis

Diagnosing RA quickly is important because early diagnosis will prevent further tissue damage and disease progression. In this context, identifying biomarkers with a diagnostic role in the early stages of the disease is important. Circulating markers of RA include the anti-cyclic citrullinated peptide (anti-CCP) antibodies, rheumatoid factor (RF), anti-mutated citrullinated vimentin (anti-MCV) antibodies and 14–3-3η protein(12).

Anti-cyclic citrullinated peptide (anti-CCP)

Anti-CCP is an antibody present in most RA patients. Levels of anti-CCP can be detected in a patient through a simple blood test. A positive anti-CCP test result can be used in conjunction with other blood tests, imaging tests, and/or physical examination findings to diagnose RA(13). This antibody is positive in the early stages of the disease and even before symptoms occur. In a study by *Ajeganova et al*, on 2331 patients, the results showed that the presence of anti-CCP in serum was associated with increased mortality in RA patients(14). The specificity and sensitivity of anti-CCP by ELISA were measured by *Pietrapertosa et al*, in 787 patients with RA, 1024 other autoimmune/inflammatory rheumatic diseases and 401 non-autoimmune RA patients. The results of this study showed that the increased level of anti-CCP was a more specific marker and is helpful in the differential diagnosis of this RA disease(15). Anti-CCP is not only an important diagnostic biomarker for the classification of this disease but also directly contributes to its pathogenesis by facilitating the formation of neutrophil extracellular traps (NETs) and binding to Fc receptors(16). *Demourelle et al.*, studied 340 patients for anti-CCP using CCP2IgG and CCP3.1 (second and third-generation) by ELISA assay. Results showed that in patients with RA, CCP2 was more accurate than CCP3.1 (99.2% vs. 93.1%; P <0.01) but its sensitivity was lower (58.7% vs. 67.4%; P <0.01)(17). In a Chinese population, studies showed that high titers of anti-CCP antibodies (≥100 RU/ml) with positive RF had the highest diagnostic properties, especially in the early stages of the disease(18). Improvement in diagnostic systems increased the sensitivity (60%-80%) and specificity (95%-98%) of anti-CCP antibodies in the diagnosis of RA(19).

Rheumatoid factor

The rheumatoid factor is a family of autoantibodies that recognizes the 'fraction crystallizable' (Fc) part of IgG molecules and exists as IgA-, IgG- and IgM-isotypes. RF is detected in majority of patients with established disease and constitutes one of the American Colleges of Rheumatology (ACR) classification criteria(20). RF has been the subject of intensive study, but definite conclusions on its role in RA have not been drawn. Moreover, several recent studies have generated interest in the value of positive titers of autoantibodies as markers of rheumatic diseases. The levels of RF give some indication of the prognosis, albeit a rather poor one in this highly variable disease(21). In this context, various prospective studies showed a clear association between RF at the baseline and the later development of cartilage and bone erosions(22, 23).

The results of *Bas et al*, study showed that anti-CCP and RF are similar but sensitivity to anti-CCP is more specific than IgM, IgG or IgA isotypes and RF(24). Numerous studies have shown that the combination of anti-CCP and RF is highly sensitive, especially for early detection, because antibodies complement each other (25-28).

Anti-carbamylated protein (anti-CarP)

According to previous studies, anti-carbamylated protein (anti-CarP) is present in more than 45% of patients and anti-CarP IgG and anti-CarP IgA antibodies are present in 16% and 30% of anti-CCP negative patients(29). This antibody with anti-CCP appears simultaneously in the blood 10 years before the onset of the disease and before detection of IgM isotype in the serum(30, 31). *Shi et al*, demonstrated that the presence of anti-CarP in patients with arthralgia independently of positivity for anti-CCP-2 antibodies predicts progression of RA(31). Therefore, anti-CarP may be a useful

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biomarker in the identification of anti-CCP negative patients at the pre-clinical phase of the disease. Anti-CarP screening is also important in patients who have recently been infected and need early clinical intervention(31, 32).

The results of *Scinocca et al* showed that anti-CarP is very specific for the diagnosis of this disease because it is not found in other inflammatory rheumatic patients as well as in healthy and normal subjects(33). However, *Chimenti et al*, have demonstrated that anti-CarP is present in patients with psoriasis and anti-citrullinated protein antibodies (ACPA) negative arthritis, and there is a relationship between anti-CarP levels and disease activity in inflammatory polyarthritis patients with RF and anti-CCP are negative(34). The results of the *Muller et al*, showed that anti-CarP was found in adolescent idiopathic arthritis (JIA) patients. In this study, JIA patients were positive for at least one of the anti-CarP (16.7%), anti-CCP (6.4%), anti-carbamylated-FCS (anti-Ca-FCS) (8.1%) and anti-carbamylated-Fibrinogen (anti-Ca-Fib) (13.2%) antibodies. Also 53% of ACPA positive and 42.1% of rheumatoid Factor IgM (RF-IgM) positive patients were anti-CarP positive(35).

Anti-mutated citrullinated vimentin (anti-MCV)

Anti-mutated citrullinated vimentin (anti-MCV) antibodies are a member of the ACPA family and a part of RA diagnostics, especially in sera negative for RF and have been recommended to be better diagnostic marker for early arthritis(36). A meta-analysis of anti-MCV and anti-CCP sensitivity and specificity was done by *Lee et al.*, and their results showed that anti-MCV sensitivity was higher than anti-CCP but anti-CCP is more specific (anti-MCV sensitivity and specificity was 68.6% and 94.2%, compared to anti-CCP sensitivity and specificity 61.7% and 97.1%, respectively). Accordingly, the diagnostic accuracy of anti-MCV is lower than that of anti-CCP(37). The results of a study by *Sun et al* also showed high sensitivity and low specificity of anti-MCV versus anti-CCP, and found that 3 combinations of CCP + MCV, CCP + RF, and CCP + RF + BIP (Immunoglobulin Binding Protein) were valuable in the diagnosis of disease(38). Comparison of anti- MCV with anti- CCP and RF with respect to sensitivity, specificity and the area under the curve (AUC) against disease controls for differential diagnosis have shown that anti-MCV has comparable diagnostic value to anti-CCP and RF, thus it can be an effective diagnostic marker for RA and may be written into the next authoritative criteria(39).

14-3-3η protein: a promising biomarker for rheumatoid arthritis

14-3-3η protein is a joint-derived, pro-inflammatory mediator that is implicated in the joint erosion process and pathogenesis of RA. Serum 14-3-3η is elevated in both early and established RA. A study was designed by *Xun et al*, on 259 RA patients, the results showed that 14-3-3η protein levels were significantly elevated in patients, especially in the early stages of the disease(40). Accordingly, these patients are immune from adverse effects of delayed diagnosis. *Shovman et al.*, assessed the prevalence and serum levels of 14-3-3η in patients with RA and in patients with other rheumatic diseases and demonstrated that the prevalence of 14-3-3η positivity in patients with early RA was 58%, significantly higher than that in disease controls and healthy subjects(41). *Maksymowych et al.*, investigated the sensitivity/specificity for the combination of 14-3-3η/anti-CCP (0.71/0.92) and RF/anti-CCP (0.71/0.84) in RA patients(42). This study was performed on 234 patients (99 of them were in the early stages of the disease) and the results were compared with a control group (n=385). According to their study, when the sensitivity is the same, the specificity of the combination of 14-3-3η and anti-CCP is much greater than combination of the RF and anti-CCP(42).

Biomarkers based on proteomic and peptidomic studies

ZHENG et al, studied the serum levels of RA patients and control groups (age range, 39-76 years). The results of proteomic and peptidomic studies showed that cytoskeletal proteins such as actin, dermcidin, serum amyloid A and talin were higher than that of the control group. They also showed that some proteins such as C-reactive protein (CRP) and actin are present in non-glycopeptide segments. Peptide analysis showed that calgranulin A (S100A8), calgranulin B (S100A9) and calgranulin C (S100A12) were present in all glycoprotein sections(43).

Human coactosin-like 1 (COTL1) protein is similar to Dictyostelium discoideum coactosin (44). The COTL1 gene is located on chromosome 16q24.1. Human COTL1 protein is a small protein composed of 142 amino acid residues with a molecular mass of 17 kDa. Human COTL1 was also identified as a

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filamentous actin (F-actin) binding protein in transfected CHO and COS-7 cells and as a 5-lipoxygenase (5LO) binding partner in a yeast two-hybrid screen(44, 45). 5LO is the first committed enzyme of leukotrien biosynthesis. The LKKAET-like motif of COTL1 interacts with 5LO involved in leukotriene biosynthesis in the leukocytes(46, 47). *Jin et al.*, compared protein levels in patients (n = 455) and healthy control (n = 568) by two-dimensional gel electrophoresis (2-DE) and MALDI-TOF mass spectrometry. Results showed that COTL1 was found in patients. It is expressed more frequently than healthy individuals(48).

Bo et al., studied the synovial fibroblast proteins of osteoarthritis and RA patients by 2-DE technique then western blot technique was used to confirm the results. The results showed that the expression levels of Enolase α, S100A4, S100A10, Annexin I (Anx-1), Cathepsin D, mitochondrial superoxide dismutase (MnSOD) and peroxire-doxin 2 (PRX2) were significantly increased in the synovial fibroblasts of both patients groups in compared to the control group(49). The remarkable point was that the results were consistent with proteomic analysis. They also demonstrated that the expression levels of Cathepsin D and MnSOD were higher in osteoarthritis patients than RA patients(49). In another study, *Zhang et al.*, investigated synovial fibroblasts in patients with osteoarthritis and RA by 2-DEMS and Western blot and demonstrated that PIMT and pirin expression were lower in RA patients but Trx-1 is only expressed in RA patients(50).

Katano et al., showed (by MALDI-TOF mass spectrometry) that neutrophilgelatinase-associated lipocalin (NGAL) in the synovial fluid of RA patients was significantly higher than in osteoarthritis patients. Also, in osteoarthritis patients, this protein is strongly expressed in neutrophils(51). They also found that NGAL levels in the synovial cells of RA patients were significantly higher than osteoarthritis patients(51). *Schulz et al.*, demonstrated that the majority of the proteins differentially expressed in RA patients when compared with healthy controls can be detected as protein fragments in peripheral blood mononuclear cells (PBMCs) obtained from RA patients. This set of deregulated proteins includes several factors that have been shown to be autoantigens in autoimmune diseases(52).

Giusti et al., compared the saliva proteins of 20 patients with 20 healthy individuals by 2-DE mass spectrometry technique. In this study, the expression of 8 salivary proteins was different between the control and patient groups. They evaluated expression of calgranulin A, calgranulin B, apolipoprotein A-1, 6-phosphogluconate dehydrogenase, peroxiredoxin 5, epidermal fatty acid-binding protein, GRP78 and 14-3-3η proteins and among these proteins chaperone GRP78/BiP showed the greatest increase in RA patients(53). Proteomic analysis also revealed that Grp78 is one of the antigens associated with anti-CCP(54). *Lu et al.*, demonstrated that Grp78 protein levels were increased in patients, and anti-CCP increased nuclear factor-κB (NF-κB) activity and tumor necrosis factor α (TNFα) production in monocytes or macrophages by binding to surface- expressed citrullinated Grp78.

Biomarkers to Predict Treatment Response

A reasonable assumption was that the clinical and laboratory markers used to establish the diagnosis or prognosis of RA might also help to predict the treatment response (table 1). However, numerous studies in patients given TNF antagonists showed that the only markers in this group of potential usefulness as treatment response predictors were the Health Assessment Questionnaire (HAQ) score, IgA-RF, and ACPAs (55). RFs and ACPAs are powerful biomarkers in the diagnosis of RA and are closely associated with a good response to rituximab or abatacept. However, the results of a meta-analysis have shown that these biomarkers are not efficient to predict the response to TNF antagonists (55-58). Based on previous studies, there is no convincing data indicating that biomarkers such as RFs and ACPAs can correctly predict treatment response, although it has been well established that the simultaneous use of several parameters can be applied to the individual patient (59). In 3280 patients given golimumab for RA, a combination of six baseline parameters [male gender, younger age, lower HAQ score, CRP level or ESR, tender or swollen joint count, and absence of comorbidities was effective in predicting remission or low disease activity(59). The results of *Kastrinaki et al.*, showed that apolipoprotein A-1 was predictive of a good response to infliximab, whereas platelet factor 4 was associated with non-responders(60). Baseline TNF-α levels are associated with the dose required for infliximab to achieve the

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highest clinical response(60). Tocilizumab affects the IL-6 receptor, thus clinical response to tocilizumab is correlated with IL-6 receptor level(61).

methods of determining disease activity is very important and may be useful for clinical evaluation(66). Previous studies have shown that high concentrations of anti-CCP and RF increase

Table 1. Biomarkers of rheumatoid arthritis (43, 48, 49, 62-65)

Biomarker	Types	Function
Actin	cytoskeletal elements	muscle contraction, cell motility, cell division
Apolipoprotein A-1	Plasma protein	lipid metabolism
Calgranulin A, B, C,	Plasma protein	differentiation, cell cycle regulation, Ca2+ homeostasis,
COTL1	Plasma protein	Binds to F-actin
CRP	Acute phase protein	Systemic inflammatory response
EGF	Growth Factor	Cellular influx and tissue expansion
IL-6	Cytokine-related protein	Local inflammation and destruction
Leptin	Hormone	Systemic inflammatory response
MMP-1	Matrix metalloproteinase	Cartilage destruction and joint damage
MMP-3	Matrix metalloproteinase	Cartilage destruction and joint damage
Resistin	Hormone	Systemic inflammatory response
thymosin β4	Plasma protein	intracellular G-actin sequestering peptide
TNF-R1	Cytokine-related protein	Local inflammation and destruction
Tubulin	cytoskeletal elements	required for DNA segregation
VCAM-1	Adhesion molecule	Cellular influx and tissue expansion
VEGF-A	Growth Factor	Cellular influx and tissue expansion
vimentin	cytoskeletal elements	stabilize cytoskeleton interactions
YKL-40	Skeletal-related protein	Stromal activity and regulation
SAA	Acute phase protein	Systemic inflammatory response

COTL1: Coactosin Like F-Actin Binding Protein 1; **CRP:** C-reactive protein; **EGF**: epidermal growth factor; **IL-6**: interleukin -6; **MMP-1**: Matrix metalloproteinase-1; **MMP-9**: Matrix metalloproteinase-9;**SAA**: Serum amyloid A; **TNF-R1**: Tumor necrosis factor receptor 1; **VCAM-1**: Vascular cell adhesion protein 1; **VEGF-A**: Vascular endothelial growth factor A; **YKL-40**: Chitinase-3-like protein 1

Biomarkers for the disease activity in Rheumatoid arthritis

Disease activity leads to continued destruction of the joints. Therefore, understanding the

disease and decrease the chance of recovery with time in men treated with disease-modifying anti-rheumatic drugs (DMARDs) (67, 68). In a study conducted by *Li et al.*, on 112 patients with RA

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and 55 non-RA, the results showed an association between anti-CCP and DAS28 score (r = 0.404, P <0.001) and RF in 560 RA patients had a moderate relationship (r = 0 / P <0.001), while there was no relationship between anti-CCP and patient age and disease duration. This association between anti-CCP with disease activity score-28 (DAS28) and RF has made this antibody a potential marker for evaluation of disease activity and also used in combination with RF in the diagnosis of disease. On the other hand, in non-rheumatoid patients, anti-CCP antibody titers were not significantly correlated with patient age, disease duration, RF, CRP, and DAS28(18). *Shovman et al.*, investigated the correlation between changes in serum 14-3-3η levels and changes in clinical disease activity measures in RA patients treated with tofacitinib (TOF) and showed that in RA patients who were treated with TOF, decrease in 14-3-3η levels was correlated with improvement in clinical disease activity parameters(69).

Increases in some disease activity parameters such as erythrocyte sedimentation rate (ESR) and CRP in these patients have been proven in the past. *Keenan et al.*, showed that ESR and CRP had a weak correlation with disease activity in RA, lupus erythematosus (SLE) and osteoarthritis (OA) patients(70). An additional main problem is that more than 40% of RA patients at presentation have normal ESR or CRP(71). Accordingly, research on the new parameter like platelet indices has recently expanded, although there is very little evidence and no definitive results have been obtained.

Prognostic biomarkers in Rheumatoid arthritis

The results of the study by *Liao et al* showed that CRP, S100A8, S100A9, and S100A12 increase the erosive form of the RA disease(63). The presence of RF and its high titer are associated with an increased risk of the disease, so that individuals in the general population with elevated RF have up to 26-fold greater long-term risk of RA(72). Another study found that the presence of the IgA isotype was associated with greater articular cartilage(73). In patients with a positive RF, the disease progresses more rapidly and there is more functional disorder(74). Study of 279 patients in early stage of the disease showed that the presence of anti-CCP antibodies was strongly associated with radiologic progression and severity of disease than predicted RA(75). Other prognostic biomarkers, such as anti-MCV and14-3-3η protein, are associated with an increased severity of RA and are not commonly tested(76).

Conclusions

Finding a new biomarker with clinical application has become a serious issue in RA patients. Based on previous studies, it can be concluded that the anti-CCP biomarker is very suitable for the diagnosis of RA. In addition to biomarkers such as RF and anti-CCP, evaluation of anti-MCV can be a useful tool in the early diagnosis of RA. Despite individual increases in serum 14–3-3η, anti-CCP, anti-MCV and RF, the combination of anti-CCP and anti-MCV might be of great help for the diagnosis of RA, and so should be considered as routine tests for this disease. Apart from the antibodies that help establish the diagnosis and prognosis, also novel biomarkers that reflect clinical disease activity scores are being discovered. The development of biomarker-based disease activity scores might allow easy and frequent monitoring of patients to rapidly adjust treatment. Although the identification of a biomarker that can correctly predict treatment response in RA patients remains a problem, but the use of matrices made from different biomarkers can help predict the treatment response in individual patients. In general, the biomarkers that have been discovered could not determine definitively the RA, its progression and response to treatment.

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Conflict of Interests

The authors report no conflicts of interest.

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مقاله مروری

نقش نشانگرهای زیستی در تشخیص، پیش آگهی، درمان و تعیین فعالیت بیماری در آرتریت روماتوئید

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چکیده

آرتریت روماتوئید (RA) یک بیماری التهابی مزمن و خود ایمنی است. این بیماری به طور عمده بر مفاصل کوچک (دست و پا) تأثیر می گذارد و تظاهرات سیستمیک زیادی دارد.

مطالعه ی نشانگرهای زیستی در روماتولوژی از ضروریات درک مکانیسم درگیر در برخی از بیمارهای روماتیسمی است. کشف نشانگرهای زیستی جدید با نقش‌های کلیدی در مراحل مختلف بیماری به عنوان یک موضوع مهم در بیماران RA باقی مانده است. نشانگرهای زیستی برای تشخیص و پیش آگهی، درمان هدفمند و هدایت درمان بالینی و پاسخگویی در تمام مراحل RA مهم هستند. نشانگرهای زیستی با بستن شکاف سرولوژیکی، تشخیص را بهبود می‌بخشند، اطلاعات پیش آگهی را ارائه می‌دهند و اجازه کنترل فعالیت بیماری و پیشرفت آن را فراهم می‌کند. نشانگرهای زیستی با خطر پیشرفت RA ارتباط دارند و می‌توانند فرسایش استخوانی و پیشرفت بیماری را پیش بینی کنند. بنابراین برای تشخیص زود هنگام بیماری نیاز به نشانگر زیستی حساس است. برخی از نشانگرهای زیستی اختصاصی نیستند (فاکتور روماتوئید IgM) و بعضی دیگر به دلیل مشکلات فنی کاربرد زیادی ندارند (فاکتور ضد ترشحی هسته‌ای). از طرف دیگر آنتی بادی‌هایی که بر علیه پپتیدهای سیترولینه (anti-CCP) در سرم بیماران وجود دارد برای این بیماران اختصاصی تر عمل می کند. حرکت از رویکردهای سنتی و استفاده از نشانگرهای ویژه تری برای طبقه بندی بیماران و درمان هدفمند، مراقبت از بیمار را بهبود و هزینه های پزشکی را کاهش می‌دهد.

کلمات کلیدی: آرتریت روماتوئید، نشانگر زیستی، تشخیص، پیش آگهی، فعالیت بیماری

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