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Biomarkers in the diagnosis, prognosis and management of rheumatoid arthritis: A comprehensive review

Didem Sahin[1,2], Andrea Di Matteo[1,2] and Paul Emery[1,2]

Abstract

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune condition that primarily affects the joints and periarticular soft tissues. In the past two decades, the discovery of new biomarkers has contributed to advances in the understanding of the pathogenesis and natural history of RA. These biomarkers, including genetic, clinical, serological and imaging biomarkers, play a key role in the different stages and aspects of RA, from the so called 'pre-clinical RA', which is characterized by subclinical pathological events, such as autoimmunity and inflammation, to diagnosis (including differential diagnosis), treatment decision making and disease monitoring.

This review will provide an overview on the current role of traditional and newer biomarkers in the main aspects of RA management, from the identification of individuals 'at-risk' of RA who are likely to progress to clinically evident disease, to 'early' diagnosis of RA, prognosis, precision medicine, and prediction of response to treatment.

Keywords

Rheumatoid arthritis, biomarkers, autoantibodies, cytokines

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune condition that primarily affects the joints and periarticular soft tissues.[1] The prevalence of RA is approximately 1% in the adult population.[1] Females are more affected than males with a ratio of 2.45.[2] RA has significant negative impact on patient's quality of life. Indeed, if left untreated, RA leads to irreversible joint damage, development of extra-articular manifestations, disability, and increased mortality.

An early diagnosis and prompt treatment initiation, especially when poor prognostic factors are present, are crucial for optimal management of RA patients.[3] In 2010, the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) updated their classification criteria for RA; four main domains were delineated, including joint involvement (i.e. number of joints and small vs large joints), serology (i.e. RA-related autoantibodies), acute phase reactants (APRs), such as increased C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), and duration of symptoms (i.e. more or less than 6 weeks).[4,5]

The development of a swollen joint is traditionally regarded as the beginning of RA. In recent years, the concept of RA as a 'disease continuum' has emerged. According to this concept, RA starts with a pre-clinical phase, in which individuals 'at-risk' of this disease (because of the presence of genetic/environmental risk factors) go through different phases of autoimmunity and sub-clinical inflammation,

[1]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals, NHS Trust, Leeds, UK
[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK

Corresponding author:
Paul Emery, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Leeds LS7 4SA, UK.
Email: p.emery@leeds.ac.uk

before evolving into a chronic (and clinically evident) disease state.[6] This RA 'disease continuum' encompasses complex disease mechanisms and diversity in immune cell profiles among individual patients. In the past decade, multiple studies have attempted to prevent the development of RA (or delay its onset) in individuals 'at-risk', with some encouraging results.[7] An important aspect to take into consideration is that not all 'at-risk' individuals will develop clinical RA. Therefore, the identification of reliable biomarkers is crucial for the risk-stratification of these individuals (i.e. differentiation between those at low-risk and those at high-risk of developing the disease) and their management, including consideration for participation in prevention trials.

The management of RA has undergone significant advances over the last two decades. Our understanding of the RA pathogenesis has improved considerably, so has the ability to diagnose RA patients early, using biomarkers including serum and imaging. Cutting-edge treatments have been developed to selectively inhibit specific immune cells or cytokines, making a treat-to-target approach feasible. Nevertheless, in some patients, achieving a status of disease remission can be challenging, highlighting the complexity and heterogeneity of RA. Addressing this heterogeneity is essential for optimizing the therapeutic management of RA patients (i.e. precision medicine).

Therefore, the field of biomarker research in RA holds great promise for improving patients long-term outcomes. From new genes being discovered to autoantibodies, serology and advanced imaging techniques, the range of available biomarkers continues to expand. This review will provide an overview on the status of traditional and new biomarkers in the diagnosis (including the identification of 'at-risk' individuals) and management of RA, including prognosis, precision medicine, and treatment monitoring. In addition, the role of each biomarker in different stages of RA continuum are summarized in Table 1.

Biomarkers

Genetic biomarkers

The likelihood of developing RA is influenced by genetic factors. Multiethnic genome-wide association studies revealed more than 100 genetic loci associated with RA, highlighting the polygenic nature of the disease.[8–11] The familial heritability of RA is around 60%, and is more prominent in younger and seropositive RA patients than in older and seronegative patients (i.e. 50% for anti-citrullinated protein antibodies (ACPA) positive RA and 20% for ACPA negative RA).[8,10] The HLA-DRB1 allele, also called shared epitope (HLA-SE), has been traditionally regarded as the most important genetic risk factor for RA development.[12,13] HLA-SE has a strong association with ACPA, and studies have shown an allele-dose effect on the levels of these antibodies.[14–18] Smoking exposure in combination with two copies of HLA-SE increases significantly (20-fold) the risk of developing RA.[14,16,19,20] Nevertheless, HLA-SE explains only 18% of the genetic variance in ACPA positive RA, and only 2.4% of ACPA negative RA.[21] On the other hand, some HLA-DRB1 alleles have showed a protective effect on the disease development, such as HLA-DRB1*1301, HLA-DRB1*1302, and DERAA-encoding HLA-DRB1 alleles.[22–25]

The presence of HLA-SE has been associated with radiographic progression.[26–28] A previous study highlighted a robust association between the presence of valine at position 11 of the HLA-DRB1 gene and increased susceptibility to radiological damage.[29] On the other hand, the impact of HLA-DRB1 presence on the response to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biological DMARDs (bDMARDs) remains uncertain.[29–34] Similarly, while one study found no correlation between HLA-SE and disease remission with csDMARD therapy, another demonstrated that the absence of HLA-SE predicted DMARD-free remission in RA patients.[31,35] Finally, certain HLA-DRB1 alleles were found to be associated with RA extra-articular manifestations (i.e. Felty's syndrome and rheumatoid vasculitis) and increased mortality.[29,36,37]

Other than the HLA-SE, the protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene has been reported to be an important genetic risk factor for RA. PTPN22 encodes for lymphoid tyrosine phosphatase (LYP), which is a 110-kd protein and a critical regulator of T-cells, B-cells and other immune cells activation.[38] The single nucleotide polymorphism (SNP) rs2476601 in the PTPN22 gene has been consistently associated with an increased risk of RA.[39,40] This variant results in the substitution of arginine with tryptophan at position 620 (R620W) in the LYP protein.[38] The altered function of LYP has been implicated in dysregulated immune responses, contributing to the pathogenesis (via augmented T cell signalling) of RA. In a retrospective study on blood donors, the polymorphism in PTPN22 along with ACPA positivity predicted future development of RA, with a specificity of 100%.[41] Variable predictive values were reported for the progression from undifferentiated arthritis to RA.[42–44] PTPN22 was found to be associated with an earlier disease onset and ACPA positivity in multiple studies,[18,45] as well as with baseline radiographic erosions and radiographic progression.[46] However, no correlation was found between this gene and treatment response to methotrexate or tumour necrosis factor inhibitors (TNFi).[47,48]

Other genes, which could potentially play a role in RA disease susceptibility, include TNFAIP3, PADI4, STAT4, TRAF1C5, and CTLA4. In addition, epigenetic mechanisms, such as DNA methylation and histone acetylation, and microRNAs, have also been implicated in the pathogenesis pathways (i.e. regulator of immune cell development and function) that are involved in the RA disease onset and perpetuation.[49,50]

Table 1. The role of each biomarker in RA.

	Pre-clinical RA	Diagnosis	Prognosis
Genetic biomarkers	Increased risk of RA development Autoantibody production	No routine use	Possible association with radiographic progression Conflicting data for treatment response Association with extra-articular manifestations (e.g. Felty syndrome and rheumatoid vasculitis)
Autoantibodies	Precede development of musculoskeletal symptoms and subclinical synovitis on US Potential link with bone loss Increase risk of RA development	2010 ACR/EULAR classification criteria (RF/ACPA)	Poor prognostic factor (i.e. association with joint damage, high disease activity, less drug-free remission and extra-articular manifestations) Possible association with response to individual bDMARDs
APRs	Increased RA risk (especially ESR)	2010 ACR/EULAR classification criteria (CRP/ESR)	Poor prognostic factor (i.e. active disease, association with joint damage, and less drug-free remission) Part of disease activity scores (i.e. DAS 28-ESR) Weak correlation with PROs
Cytokines	Increased serum levels before clinical disease No clear association with RA development	No routine use Increased levels compared to other arthritides/healthy controls	Joint damage High disease activity Target molecules for bDMARDs (i.e. TNFi and IL-6 inhibitor)
14-3-3η	No clear role	No routine use Positive correlation with autoantibodies	Possible association with radiographic progression, high disease activity, and response to tocilizumab
MicroRNAs	Increased serum levels before clinical disease	No routine use Increased levels compared to other arthritides/healthy controls	High disease activity Treatment response to DMARDs (i.e. TNFi/csDMARD combination and rituximab)
MMPs	No clear role	No routine use Increased levels compared to other arthritides/healthy controls	Association with joint damage, high disease activity
T cells	Increased RA risk (result of the dysregulation)	No clinical use	Association with treatment response (i.e. methotrexate), drug-free remission
Imaging	Increased RA risk (subclinical synovitis-tenosynovitis-erosions)[a]	1987 ACR classification criteria (erosions-periarticular osteopenia on X-Ray) Additional criteria 2010 ACR/EULAR classification criteria Helpful in differential diagnosis	Joint damage evaluation[b] Joint damage prediction Treatment response to DMARDs Consider intensive medication when erosions present Increased risk of flares Less drug-free remission (when subclinical inflammation on US)

Abbreviations: APRs: Acute phase reactants. ACPA: Anti-citrullinated protein antibodies. ACR: American College of Rheumatology. bDMARDs: biological disease-modifying antirheumatic drugs.csDMARDs: conventional synthetic DMARDs. CRP: C-reactive protein. DAS28: Disease activity score 28. ESR: Erythrocyte sedimentation rate. csDMARD: EULAR: European Alliance of Associations for Rheumatology. IL-6: Interleukin-6. miR: microRNAs. MMPs: Matrix metalloproteinases. PRO: Patient reported outcomes. RA: Rheumatoid arthritis. RF: Rheumatoid factor. TNFi: Tumour necrosis factor inhibitors. US: Ultrasound.

[a]Ultrasound and/or magnetic resonance imaging detected.

[b]X-Ray, ultrasound or magnetic resonance imaging.

Autoantibodies

Anti-cyclic citrullinated peptide antibodies and rheumatoid factor. Autoantibodies play a key role in the pathogenesis of RA. Different autoantibodies target different and specific antigens. ACPAs and rheumatoid factor (RF) represent specific and early serological markers for the diagnosis of RA. ACPAs are a group of antibodies directed against proteins (such as filaggrin, vimentin, α-enolase, and fibrinogen) that have undergone citrullination, which is a post-translational modification where the amino acid arginine is converted to citrulline.[51] On the other hand, RF is an

autoantibody primarily of the IgM class, which targets the Fc portion of IgG antibodies, forming immune complexes that can contribute to tissue damage and inflammation. For ACPA detection, second-generation anti-cyclic citrullinated peptide (CCP2) assay is widely used in Europe, while third generation anti-cyclic citrullinated peptide (CCP3) are commonly used in the United States. The technological differences between CCP2 and CCP3 assays are not completely known as they've not been disclosed by the companies (e.g. targeted antigens).

ACPA and RF are important diagnostic biomarkers. Indeed, the presence of ACPA and/or RF is one of the four cardinal features of the 2010 ACR/EULAR classification criteria for RA.[4] The frequency of ACPA and/or RF positivity in the general population has been reported to range from 1% to 2.8%.[52,53] ACPA showed similar sensitivity but higher specificity than RF for the diagnosis of RA (67% vs 69% and 95% vs 85%, respectively).[54]

ACPAs and RF can precede the development of RA by up to 18 years.[55] The detection of these autoantibodies, especially ACPAs, has been associated with an increased risk of developing RA in different 'at-risk' populations.[56–59] In a previous study of our research group involving different 'at-risk' individuals with musculoskeletal symptoms, a positive anti-CCP3 antibody test increased significantly the risk of developing RA.[60,61] Conversely, a negative anti-CCP3 test in these anti-CCP2 positive individuals decreased remarkably the risk of developing RA, especially in those with high titer anti-CCP2 antibodies. Subsequently, in a similar population of anti-CCP2 positive 'at-risk' individuals with musculoskeletal symptoms (with no clinical or sub-clinical joint involvement), anti-CCP3 antibodies were associated with the development of joint inflammation on ultrasound (US).[62] The presence of ACPA has also been linked with bone loss in individuals 'at-risk' of RA, long before the onset of clinical synovitis.[63,64] Interestingly, in a population-based study including ACPA IgG-positive healthy individuals, the presence of different ACPAs/RF isotypes (e.g. ACPA IgA) and other autoantibodies was associated with the development of clinically suspect arthralgia.[65] ACPAs have also showed a distinct association with different T-cells profiles in patients with early RA. In a study, lower naive and regulatory T cells (Tregs) frequencies were found in ACPA+ 'at-risk' individuals than in those without autoantibodies.[66]

RA-related antibodies have also been associated with a more aggressive RA disease phenotype, which is characterized by more joint damage, higher disease activity, and extra-articular manifestations.[67–73] Previous studies have shown that seropositive RA patients could potentially respond better to certain bDMARDs, particularly rituximab and abatacept, and to some extent tocilizumab, than to TNFi.[48,74–76] Positive results in terms of treatment response have also emerged in seropositive RA patients who are treated with tofacitinib, which is a Jak-inhibitor.[77] Other studies have also revealed that seropositivity was associated with good treatment response, but less long-term drug free remission in early RA patients.[78,79] An important aspect to consider is that the levels of antibodies may fluctuate (particularly RF), primarily due to changes in medication intensity, but this has less impact on disease activity indices and long-term outcomes.[80] Additionally, seroconversion (i.e. negativization of autoantibodies) appears to be a very rare occurrence in RA patients, also in those who have achieved persistent and drug-free remission.[81] These results emphasize the dynamic picture of RA pathogenesis and management.

Other novel autoantibodies. Anti-Carbamylated Protein Antibodies (anti-CarP) antibodies target proteins that have undergone non-enzymatic post-translational modification, where cyanate binds to lysine residues, forming homocitrulline.[82] In contrast to ACPAs, no associations have been found between HLA-SE and anti-CarP antibodies, emphasizing the diverse nature of the immune responses and antibody profiles involved in the pathogenesis of RA.[83]

Studies in preclinical RA demonstrated that, like RF and ACPAs, anti-CarP antibodies can be identified in the serum of 'at-risk' individuals years before the diagnosis of RA. However, adding anti-CarP to conventional antibodies (i.e. RF and ACPAs) did not improve the prediction for progression to RA in a study.[84]

Anti-CarP antibodies can be found in 30%–47% of established RA and can be detected in both seropositive and seronegative (i.e. for RF or ACPAs) patients.[85–89] Anti-CarP seems to play a relevant role especially in ACPA negative patients, where they might be useful for RA classification.[88] In a meta-analysis, triple positivity for RF, ACPAs, and anti-CarP showed a very high specificity for the diagnosis of RA (98%–100%), in spite of a sub-optimal sensitivity (11%–39%).[90]

Positive anti-CarP antibodies were found to be associated with worse radiographic outcomes in both ACPA positive and negative RA patients, as well as in individuals 'at-risk'.[91]

Elevated levels of anti-CarP antibodies and anti-peptidylarginine deaminases-4 antibodies (anti-PAD4) were associated with poorer response to TNFi.[92] Another study showed a positive correlation between the presence of anti-CarP antibodies and response to abatacept.[87]

Another novel class of autoantibodies identified in RA is anti-PAD4. Increased levels of anti-PAD4 were detected in the serum samples of the patients before RA development.[93] A recent meta-analysis showed a pooled sensitivity of 34% and specificity of 94% for RA diagnosis.[94] When combined with ACPA, a slight improvement in the sensitivity was observed compared to ACPA alone (3.8%).[94] Positive anti-PAD4 was also shown to be associated with radiographic joint damage in RA patients.[95,96]

Antibodies against other post-translational modifications have also been described, including anti-acetylated protein

antibodies and anti-malondialdehyde-acetaldehyde antibodies, mainly in ACPA positive patients.[97,98] However, their additional value in comparison to the more traditional anti-CCP and RF is unclear; therefore, they are not used in routine clinical practice.

Acute phase reactants

C-reactive protein and erythrocyte sedimentation rate. CRP is an acute phase protein, which is produced by the liver in response to inflammatory stimuli. In RA, the production of pro-inflammatory cytokines, particularly interleukin-6 (IL-6), leads to an elevation of CRP levels.[99]

CRP is a useful biomarker for the diagnosis and assessment of disease activity of RA patients. Indeed, the presence of elevated APR, such as CRP and/or ESR, represents a main domain of the 2010 ACR/EULAR classification criteria for RA.[4] Previous studies have demonstrated that elevated CRP levels may occur in the preclinical stages of RA.[100] However, conflicting results were found regarding the predictive value of CRP levels for progression to clinical synovitis in different at-risk populations.[57,59,101] This might stem from its short half-life, mainly reflecting the current presence of inflammation rather than more chronic or slowly developing processes.

CRP level is a component of various comprehensive measures of disease activity, such as the *Disease Activity Index 28* (DAS28)-CRP score, *Simplified Disease Activity Index* (SDAI), and ACR/EULAR Boolean definition of remission.[102–104] Higher serum CRP levels showed a positive correlation with joint inflammation.[105] However, CRP levels are not invariably elevated with RA disease activity. For example, in a large cohort of RA patients with high disease activity according to *Clinical Disease Activity Index* (CDAI), more than half of these patients had normal CRP levels.[106] Additionally, joint inflammation on histology has been noted in nearly half of RA patients with normal CRP levels.[105] Moreover, CRP and ESR demonstrated a weak correlation with subjective measures of RA disease activity reported by patients, such as early morning stiffness and global pain, and fatigue.[107] In addition, CRP level is not a reliable indicator of inflammatory activity in patients using IL-6 blockers by blocking IL-6 to induce hepatic acute phase response.[108] These results underscore the complexity of RA, and the importance of a multifaceted approach in the assessment and management of RA patients.

Monitoring CRP levels can have a potential utility in the RA prognosis and guiding treatment. Higher baseline CRP levels were linked to radiographic joint damage and disability in different RA populations.[71,72,109] According to EULAR, an elevated CRP should be considered in treatment decision-making of RA patients (i.e. consideration of bDMARDs in patients who failed a csDMARD instead of combination therapy with two csDMARDs).[110]

ESR evaluates the rate (mm/h) at which red blood cells settle in plasma within a vertical tube. Like CRP, ESR is regarded as a non-specific inflammatory biomarker. However, unlike CRP, ESR levels can also be influenced by other factors, such as age, sex, immunoglobulin levels, and anaemia.[111] Furthermore, ESR response is slower than CRP to resolve due to longer half-life of components.[111]

An increased ESR was shown to be independently associated with RA development in a large population of CCP2 + at-risk individuals.[112] Similar to CRP, ESR is used for disease monitoring, as part of the DAS28-ESR score.[103] Elevated ESR levels are regarded as poor prognostic factors in RA patients.[73,110] Systematic reviews and meta-analyses showed an association between baseline ESR levels and poorer response to both csDMARD and bDMARD therapy.[113,114]

In conclusion, APRs such as CRP and ESR play a key role in the diagnosis and monitoring of RA patients. ESR is more complex with multiple causes for elevation but because of this more sensitive at presentation than CRP. However, CRP and ESR levels might differ and contribute separately to predicting outcomes in RA patients.[106] Therefore, in our opinion, it is important in routine practice to assess both these inflammatory markers in RA patients.

Serum calprotectin. Calprotectin, also known as S100A8/A9 or MRP8/14, is a heterodimeric complex composed of two subunits, S100A8 and S100A9, which contributes to chemotaxis, phagocyte migration, and macrophage activation.[115] It has been shown that serum calprotectin levels increase during the preclinical stages of RA.[116] A study by Baillet et al., showed higher calprotectin levels in synovial fluid of RA patients compared to osteoarthritis and other inflammatory arthritides.[117] In addition, higher calprotectin levels were detected in erosive RA compared to non-erosive RA.[118] Several studies have also demonstrated a good correlation between serum calprotectin and disease activity markers, such as DAS28-CRP and US detected synovitis.[119–122]

Data regarding the impact of baseline calprotection levels to treatment response are inconclusive.[120,123] In a large cohort study involving 470 RA patients treated with either adalimumab or etanercept, baseline calprotectin levels did not offer any additional value for the prediction of TNFi treatment response over CRP levels.[122] However, in a different study, reduced calprotectin levels after 1 month of bDMARD therapy were associated with better treatment response at 12 months.[119] Other studies explored the link between baseline calprotectin levels and RA flares in RA patients who were in sustained remission, producing controversial results regarding the effectiveness of calprotectin as a predictor for future flares in RA patients.[124–127]

Serum Amyloid A. Serum Amyloid A (SAA) is an acute phase protein which is produced primarily by the liver in response to inflammation. Serum concentration of SAA can

increase dramatically (by up to 1000-fold or more) in patients with inflammatory conditions.[128] Higher serum SAA levels were found in RA patients compared to healthy controls and patients with osteoarthritis.[128] SAA also contributes to the formation of the 'rheumatoid pannus' (i.e. hyperplasia of the normal synovial tissue, neovascularization, and a heterogeneous inflammatory cell infiltrate) and joint destruction by activating cytokines, inducing adhesion molecules expression and matrix degradation.[128,129] In a recent systematic review and meta-analysis, which included a large number of RA patients and healthy controls, SAA levels were found to be higher in RA patients, showing a significant correlation with DAS28, APRs (i.e. ESR and CRP) and inflammatory cytokines in these patients.[130] Furthermore, in the same systematic literature review, it was shown that the SAA 1.3 allele could determine an elevated risk of developing RA in 'at-risk' individuals, and RA-associated amyloidosis in patients with established disease.[130]

Cytokines

Cytokines, such as tumour necrosis factor α (TNF-α), IL-6, IL-1, IL-8, IL-17, IL-23, and GM-CSF, play a key role in the pathogenesis of RA. Interestingly, abnormal levels of cytokines and chemokines have been found in pre-clinical RA; their increase, however, has been observed later than the development of RA related autoantibodies.[55] Increasing evidence suggests that pro-inflammatory cytokines contribute to initiation and perpetuation of systemic inflammation in 'at-risk' individuals. TNF-α and IL-6 have been the most extensively studied and characterized cytokines in the pathogenesis of RA.

TNF-α is produced by macrophages, neutrophils, and activated T cells. TNF-α exerts multiple actions, including activating immune cells, stimulating production of other cytokines, and triggering tissue remodeling and bone resorption via stimulating osteoclasts, thus contributing to the development of bone erosions.[131] Serum levels of TNF-α increase in patients with active RA.[132] Consequently, molecules targeting TNF-α, so called TNFi, such as infliximab, adalimumab, etanercept, certolizumab, and golimumab, have been developed and have been used for more than two decades in RA patients. These agents have revolutionized the outcome of most RA patients, especially those who failed multiple csDMARDs. The safety of TNFi has been documented in several studies, with an increasing risk of infections being the most common side effect of these medications. Interestingly, therapy with TNFi has been associated with reduced cardiovascular risk and better survival rates in RA patients.[133–136] In addition, a previous study showed that TNFi might induce repair of bone erosions compared to methotrexate.[137]

IL-6 is another abundant key cytokine in RA, which shows similar effector functions as TNF-α.[138] Additionally, IL-6 contributes to the production of APRs, such as CRP, thus leading to systemic inflammation.[99] Elevated serum IL-6 levels correlate with high disease activity in RA patients.[138,139] Agents inhibiting IL-6 include monoclonal antibodies, such as tocilizumab and sarilumab, which target both soluble and membrane-bound IL-6 receptors. These treatments have been proven to be efficacious and safe options for RA patients, also in monotherapy (i.e. without methotrexate).[136] Multiple studies have also showed the ability of IL-6 inhibition to reduce bone resorption markers, thus potentially inhibiting joint damage and inducing bone erosions repair.[140–142] Increased IL-6 levels in serum and synovial fluid indicate better responses to IL-6 inhibition.[139,143] Additionally, a study including RA patients in remission and those with low disease activity showed that low levels of IL-6 at the time of tocilizumab discontinuation were associated with a low rate of disease relapse at 52 weeks.[144]

Nevertheless, neither TNF-α nor IL-6 is used for diagnostic or monitoring purposes in the context of RA on a daily basis, given the fact that its levels are also found to be high in other inflammatory conditions.[145,146]

14-3-3η proteins

A crucial family of intracellular regulators, 14-3-3 proteins modulate diverse cellular processes by binding to specific proteins, with 14-3-3η eta emerging as a distinctive isoform in this family. Notably, the 14-3-3η exhibited higher levels in both synovial fluid and serum of inflammatory arthritis patients including RA, compared to healthy controls.[147] A subsequent study showed higher 14-3-3η levels in early and established RA patients compared to disease controls and healthy subjects. In this study, elevated 14-3-3η levels correlated with ACPA and RF levels.[148] A recent meta-analysis showed that 14-3-3η proteins had a pooled sensitivity and specificity of 0.73 and 0.88 for the diagnosis of RA, respectively.[149] In addition, 14-3-3η levels were associated with radiographic progression, and this was more evident in treatment-naïve early RA patients than in those with established disease.[150] Another study showed a significant association between 14-3-3η levels and higher disease activity (including elevated APRs) in newly diagnosed RA patients and baseline levels of this protein predicted response to tocilizumab.[151] All these studies highlighted the potential diagnostic and prognostic implications of 14-3-3η in patients with RA.

MicroRNAs

MicroRNAs (miR) are short, non-coding RNA molecules, which are typically composed of about 21 to 23 nucleotides; these molecules regulate post-trascriptional gene expression mainly by binding the 3' untranslated region of target messenger RNAs, thereby inhibiting their translation or

promoting their degradation. MiRNAs have been implicated in various aspects of RA pathogenesis, including immune system dysregulation, inflammation, and joint tissue destruction. Many studies have revealed miRNAs dysregulation in synovial fibroblasts,[152,153] macrophages,[154,155] and peripheral blood mononuclear cells[156] of RA patients.

In a longitudinal study including ACPA+ 'at-risk' individuals, miR-22, miR-382, and miR-486-3p levels increased when patients progressed to clinical disease compared to baseline. In addition, baseline miR-22 levels were higher in progressors to clinical disease compared to non progressors, suggesting that miR-22 could be a potential biomarker for predicting RA development.[157] In a different study, a significant upregulation of miR-103a-3p and miR-346 was observed in ACPA + first-degree relatives of RA patients and patients themselves, as opposed to healthy controls where downregulation of these microRNAs was noted.[158] In another cross-sectional study, miR-126-3p, let-7d-5p, miR-431-3p, miR-221-3p, miR-24-3p, and miR-130a-3p were elevated in ACPA + at-risk individuals and treatment-naïve RA patients compared to healthy controls.[159] In a Japanese study, high plasma concentrations of miR-24 and miR-125a-5p emerged as potential diagnostic biomarkers in both seronegative and seropositive RA patients.[160] Furthermore, the combination of miR-125a-5p, miR-24-3p, and miR-26a-5p was found to have the strongest diagnostic accuracy in Caucasian RA patients.[161] Some miRs, such as miR-24, miR-16, miR-146a, and miR-223, also showed a positive correlation with DAS28 and APRs.[160,162,163] Preliminary studies including a small number of patients also showed that miR-23 and miR-223 could potentially predict treatment response to TNFi/csDMARD combination, while other studies observed an association between high levels of miR-125 and response to rituximab.[164,165] In a randomized, double-blinded trial, higher baseline miR-27a-3p levels were associated with adalimumab-induced remission at 12 months, but not methotrexate.[166] These studies have showed the promising role of miR in the diagnosis and prognosis of RA patients.

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) constitute a group of zinc-dependent endopeptidases, which are engaged in the physiological processes of tissue remodeling and repair. Dysregulation of MMP activity leads to excessive degradation of collagen, proteoglycans, and other matrix components in the synovium, which is a key contributor to the progressive joint damage observed in RA patients.[167]

Approximately 20 distinct MMPs have been identified in humans, with MMP-1 (collagenase-1) and MMP-3 (stromelysin-1) being those most extensively studied in RA. Higher serum levels of MMP-1 and/or MMP-3 have been detected in RA patients compared to healthy controls.[168–172] In patients with RA, increased serum levels of MMP-3 were associated with higher disease activity, APRs, and more disability.[170,172,173] In early RA patients, serum MMP-3 levels at the time of diagnosis showed an association with radiographic joint damage.[169] Subsequent studies demonstrated that higher baseline levels of MMPs in newly diagnosed RA patients were predictive of radiographic damage development.[170,173]

T cells

Significant T cell abnormalities have been described in various stages of RA. T-cell subsets dysregulations, particularly those that involve CD4 + T cells, CD8 + T cells, and Tregs, play a pivotal role in the initiation and perpetuation of systemic inflammation, and the development of joint damage in RA patients.[174–176] In a study which included 103 ACPA + at-risk individuals, the inclusion of CD4 + T cells – naïve cells, Tregs, and inflammation-related cells (IRCs) – in a complex statistical model (which also considered clinical, serological, and imaging biomarkers) improved significantly the prediction of inflammatory arthritis development in these individuals.[59,177]

Changes in T cell subsets have been shown to occur before the development of clinical synovitis in 'at-risk' individuals.[177] Interestingly, normal levels of baseline naïve T-cells were associated with higher remission rates in treatment-naïve early RA patients who started methotrexate.[66] In another study, which included RA patients in sustained clinical remission, lower rates of disease reactivation after TNFi discontinuation were observed in RA patients who had normal baseline levels of naïve T-cells and Tregs, and low levels of IRCs levels.[178] In addition, increased levels of baseline IRCs predicted flares in RA patients in clinical remission who underwent csDMARDs tapering.[179] Moreover, some studies have also showed that csDMARDs and bDMARDs can determine a shift in T-cell subsets frequencies, leading to an increase in Tregs levels.[180,181] A very recent study demonstrated the value of CD4 + T cell subsets in different stages of the 'RA continuum'.[182] In this study, T-cells subsets improved prediction of inflammatory arthritis development in individuals 'at-risk', and treatment response in those with established disease, including prediction of flares after therapy discontinuation.[182]

Imaging biomarkers

X-rays. Conventional radiography (i.e. X-rays) is regarded as the traditional gold standard for the evaluation of structural damage (i.e. bone erosions and cartilage damage) in patients with RA. The presence of radiographic erosions and/or periarticular osteopenia in hand/wrist joints on X-ray was part of the 1987 ACR classification criteria for RA.[5] However, X-rays have limited sensitivity in the detection of

early changes (i.e. bone erosions) and soft tissue abnormalities (i.e. synovitis and tenosynovitis). Therefore, other imaging tools with a higher sensitivity for the detection of these findings have taken place in the diagnostic work-up of RA, such as US and magnetic resonance imaging (MRI).[183,184] Nevertheless, X-rays are still widely used in current practice and have been designated as the first-line imaging technique for the detection of RA-related joint damage by EULAR.[185]

In a study on 'at-risk' individuals with anti-CCP2 + antibodies and musculoskeletal symptoms, bone erosions on X-ray were uncommon (4.1%) and not associated with inflammatory arthritis/RA development, thus suggesting that prevention studies with DMARDs should have the potential at least to prevent **X-ray** damage in these 'at-risk' individuals.[186] In patients with undifferentiated arthritis, the presence of ≥2 erosions at baseline increased the risk of progression to RA by 53%.[187] In RA patients, the detection of erosions at the time of diagnosis has been associated with further radiographic progression and poor prognosis.[73,110,188] Prospective cohort studies also showed the association of lower baseline Sharp-van der Heijde score (a method used to quantify radiographic joint damage) with higher remission rates at 3 years, including sustained DMARD-free remission.[35,189,190]

Ultrasound. US can detect synovitis, tenosynovitis, bone erosions, cartilage damage, and tendon tears.[191] Therefore, this imaging tool is widely used in the diagnostic work-up and monitoring of RA patients. US is a bedside tool, which makes it feasible to use in everyday clinical practice. Operator dependency is the main limitation of US.

Several studies have demonstrated the predictive value for future RA development of US-detected sub-clinical inflammation and/or structural damage in different populations of 'at-risk' individuals.[192,193] In a very recent study from our research group, the detection of US synovitis and/or bone erosions in only three joints (i.e. wrists, knee and MTP5) improved prediction of inflammatory arthritis progression over and above clinical and serological markers in more than 400 CCP2 + at-risk individuals with musculoskeletal symptoms.[194] In addition, synovitis and tenosynovitis were found to be predictor of progression to inflammatory arthritis in different cohorts of 'at-risk' individuals with clinically suspect arthralgia.[195,196]

US has demonstrated to have a higher sensitivity for the detection of bone erosions than X-ray in RA patients.[183,184] The presence of bone erosions on US in certain joints (MCP 2 and 5, MTP 5 and ulnar styloid) was sensitive and specific for RA compared to other rheumatic diseases, including psoriatic arthritis (PsA), osteoarthritis, gout, as well as healthy individuals.[197] The development of bone erosions early in the disease course is regarded as a poor prognostic factor for RA by EULAR, which recommends considering a bDMARD in patients with bone erosions who have failed a csDMARD.[110] US has a very important role in the differential diagnosis between RA and other arthritides, such as PsA, crystal arthritis, and connective tissue diseases.[198–200]

The presence of subclinical inflammation on US has been documented in a substantial number of RA patients in clinical remission, showing also an association with an increased risk of flares and structural progression in these patients.[201–203] A recent systematic literature review showed a pivotal role of US in different aspects of RA patients management (i.e. diagnosis, treat to target and monitoring, including prediction of disease relapse/response to therapy).[204] Multiple studies have documented that US sub-clinical inflammation can predict disease reactivation after csDMARDs or bDMARDs discontinuation in RA patients in clinical remission.[179,205–208] Despite these promising results, the role of US in the treatment decision strategy of RA patients remains unclear. Indeed, in two recent randomized clinical trials (ARCTIC and TaSER), an US driven treat-to-target strategy was not superior to a conventional ('clinical based') approach in RA patients.[209,210]

Magnetic resonance imaging. MRI scan is able to detect synovitis, tenosynovitis, bone erosions, cartilage damage, and bone marrow oedema (BME), which is also called osteitis. Costs and time are the major drawbacks of MRI use in daily practice.

In 'at-risk' patients with clinically suspect arthralgia, the presence of baseline MRI inflammation predicted the development of clinical synovitis, with tenosynovitis being the strongest predictor, while MRI-detected erosions were not predictive for this outcome.[57,211] Furthermore, interosseous tendon inflammation on MRI scan was an early feature of ACPA+ 'at-risk' individuals in a different study, and it was also detected in early and established RA patients, but not in healthy controls.[212] In a systematic literature review, the sensitivity and specificity of MRI synovitis in the prediction of progression from undifferentiated arthritis to RA was 93% and 25%, respectively.[213] The specificity of BME was high (76%), whereas the sensitivity of this finding was 51%.[213] Higher BME scores at baseline were associated with radiographic progression (i.e. bone erosions development) in multiple studies, which also included RA patients in sustained remission.[214–217] However, in a randomized clinical trial, a treatment strategy aiming at 'MRI remission' did not show superiority to the conventional (i.e. clinically driven) treat-to-target strategy.[218] In addition, while MRI pathological features at RA diagnosis were found not to be predictive of DMARD-free sustained remission in another study, results from AVERT study showed that MRI detected bone erosions were related to flares in patients who tapered therapy with abatacept.[219,220]

Integrating biomarkers: Multibiomarker disease activity score

The multibiomarker disease activity (MBDA) score system was developed to determine disease activity in RA as it is

the cornerstone to reach sustained remission or at least low disease activity according to treat-to-target strategy.[110] MBDA scoring was developed with the combination of the serum level of 12 biomarkers (IL-6, TNF receptor type 1 (TNFR1), vascular cell adhesion molecule 1 (VCAM-1), epidermal growth factor (EGF), vascular EGF A (VEGF-A), bone glycoprotein 39 (YKL-40), MMP-1, MMP-3, CRP, SAA, leptin, and resistin). The equation used in the MBDA scoring algorithm is akin to that of the DAS28-CRP, incorporating the serum level of each biomarker for different components of the DAS28-CRP scoring system.[221] This results in a scale from 0 to 100, with higher scores indicating greater disease activity in RA patients. MBDA score was also found to be correlated with other disease activity indices, such as DAS28-ESR, SDAI, and CDAI.[222] A recent systematic review and meta-analysis demonstrated positive correlations with baseline MBDA scores and baseline DAS28-CRP and -ESR, CDAI, 28 joint-tender and swollen joint counts, CRP, and ESR.[223] High MBDA scores were shown to be strongly related to radiographic damage, independent of other predictors of this outcome, including seropositivity, CRP level and radiographic damage score at baseline.[223,224] Overall, the MBDA test represents a promising tool for assessing disease activity in RA, offering a more comprehensive and objective approach compared to individual biomarkers or composite indices.

Conclusion

The current review provides an overview on the role of different biomarkers across the RA continuum, from prediction of inflammatory arthritis development in at-risk individuals, to diagnosis (including differential diagnosis), prognosis, and monitoring of RA.

The discovery and advent of new genetic, serological, and imaging biomarkers have advanced our understanding of the pathogenesis of RA and the natural history of the disease. From this biomarker pool, only autoantibodies such as RF and ACPA, and APRs such as CRP and ESR, and imaging modalities are routinely used in clinical practice for the diagnosis and monitoring of disease activity. However, normal results in these tests do not rule out an RA diagnosis and/or active disease, especially in the early phase. A combination of clinical assessment and multiple tests, especially in patients with initially negative results, is recommended for a more accurate diagnosis and effective monitoring of RA. Consequently, precision medicine remains an elusive concept in Rheumatology, as reliable biomarkers for diagnosis, prognosis, and especially for therapy, have yet to be identified. While challenges remain, ongoing research continues to refine the role of biomarkers in predicting disease progression and treatment response, ultimately improving the quality of care for RA patients.

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ORCID iD

Didem Sahin https://orcid.org/0000-0003-3558-54000

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