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POTENTIAL BIOMARKERS OF RHEUMATOID ARTHRITIS AS A TOOL FOR RESEARCH AND DEVELOPMENT OF NEW DRUG MOLECULE: A REVIEW

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ABSTRACT: Rheumatoid Arthritis (RA) is an autoimmune inflammatory illness characterized by persistent synovial inflammation. It's the most common form of arthritis that causes inflammatory changes in the tissue of joints, destroys cartilage and bones, and affects the quality of life. This diverse disease has a wide range of disease progression and treatment responses. Because the precise origin of rheumatoid arthritis is still unknown, no medicine can ensure a full recovery. Biomarkers guide the clinical and pharmacological management of rheumatoid arthritis at all phases. This is because they can help in the monitoring of disease activity and progression, the prediction of illness beginning in at-risk patients, and the provision of predictive data. American College of Rheumatology (ACR) emphasized on initial investigation of clinical findings based on the physical data for the diagnosis of RA. Although Rheumatoid factor and anti-citrullinated protein antibodies are the two biomarkers that can be used to determine who is at risk for the condition and who has pre-clinical rheumatoid arthritis before symptoms develop, there are involvements of many genes and other proteins that have been connected to a higher risk of rheumatoid arthritis development. This review analyses potential research biomarkers for RA, focusing on biomarkers presently used in routine clinical practice addressing unresolved clinical issues.

INTRODUCTION: Rheumatoid arthritis (RA) is an autoimmune, persistent inflammatory illness [1]. with an unknown cause that affects between 0.5 and 1 percent of adults globally. However, 60% of the risk factors for RA are hereditary in nature. Gene polymorphisms, complex factors and epigenetic variables including DNA methylation and histone acetylation are the first genetic factors mentioned [2]. Environmental variables, including food, smoking, and oral health, are also risk factors [3].

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An inflammatory reaction is what the illness is first known for, followed by autoantibody activation, synovial membrane destruction, and joint injury [4]. Evidence suggests that the sooner RA patients are treated, the better their prognosis. It mainly affects the synovial tissue of joints and has many systemic manifestations. The lack of clinical symptoms in the early stage of rheumatoid arthritis creates an interest in the laboratory diagnosis of the disease.

The intense study of biomarkers in rheumatology evolved from the need to comprehend the pathophysiological underpinnings of various rheumatic illnesses. A continuing area of research for RA is the identification of novel biomarkers that play crucial roles at different phases of evolution [5]. The term "biomarker" refers to interaction parameters that provide information on

an objectively measurable physiological, biochemical or morphological change that can be assessed at the molecular, biochemical, or cellular level and that serves as an indicator of a functional biological process, a pathogenic state, or as a response to medical treatment [6]. Biological markers are physiological signals brought on by a xenobiotic, a cellular exposure, an early cellular reaction, or an innate or acquired vulnerability [7].

The European League against Rheumatism (EULAR) and the American College of Rheumatology (ACR) established the 2010 RA Classification Criteria, which provide a scoring system for RA patients that considers their medical history, physical exam, and biomarkers to standardize clinical trials. The criteria have a RA classification sensitivity of 84 percent and a specificity of 60 percent [8] besides rheumatoid factor and the anti-cyclic citrullinated peptide that is used for diagnosis.

RA, following EULAR criteria [9] new biomarkers are being developed in research to help in RA diagnosis. Recently discovered auto antigens and antibodies may aid in the early identification of disease and the prognosis of disease progression [10]. The Food and Drug Administration categorizes biomarkers into the following groups [11, 60].

Diagnostic Biomarker: This is used to identify people with a certain subtype of disease or to detect or confirm the existence of a disease or other condition. For example, HbA1c is frequently employed as the primary biomarker for detecting diabetes and prediabetes [12].

Prognostic Biomarkers: These are utilized to assess the likelihood of a clinical event, illness progression, or disease recurrence in individuals having a diagnosis of an interesting disease or medical condition. For instance: rising prostate-specific antigen (PSA) levels as a marker of prostate cancer clinical progression [13].

Safety Biomarker: These are utilized to show the possibility, existence, or degree of toxicity as an unfavorable outcome assessed before or after exposure to a medical product or from environmental factors. Transaminases, for instance, have been used as biomarkers for medicines that may be hazardous to the liver [14].

Monitoring Biomarker: A biomarker that is monitored repeatedly to determine the severity of a disease or medical condition and the presence or impact of a medicinal product or environmental contaminant. B-type natriuretic peptide, for instance, has been used to assess ventricular and vascular function in children with pulmonary arterial hypertension [15].

Pharmacodynamic Response Biomarker: A pharmacodynamic response biomarker is used to show that a person's exposure to medications or environmental factors results in a biological reaction. The International Standardized Ratio (INR) for anticoagulant therapy, which has particular importance in medication modification, is one example [16].

Ideal biomarkers must be able to be obtained from patient clinical data, give diagnostic, prognostic, and therapeutic information, and have high specificity, representatively as well as stability [17].

This paper aims to review various biomarkers that have a potential role in the initiation and progression of Rheumatoid Arthritis and may be helpful in researching and developing new drug molecules for the same.

METHODOLOGY: The material in this study was gathered from a variety of sources, including research and review papers, meta-analyses, and the proceedings of conference presentations published in journals.

Various electronic database systems were used to develop strategic search, including scientific data from PubMed, Science Direct, and Google Scholar, incorporating various keywords, such as "Biomarkers for Rheumatoid Arthritis", "Antibodies for Rheumatoid Arthritis" and "Rheumatoid factor" *etc.* A huge number of articles were available, but the articles that directly related to the topic were selected to write this review.

TABLE 1: POTENTIAL BIOMARKER FOR RHEUMATOID ARTHRITIS

Diagnostic Biomarker	ACPA (Anti-citrullinated protein/peptide antibody) MBDA (Multi-biomarker disease activity) ESR (Erythrocyte

	Sedimentation Rate)
	RF (Rheumatoid Factor)
	CRP (C-reactive protein)
Investigational Biomarker	Serum 14 3 3 eta
	Anti-mutated citrullinated vimentin (anti-MCV)
	Urine CTX-I and CTX-II
	Serum COMP
	Serum hyaluronan
	Serum MMP-1 and MMP-3
	Anti-carP
Genetic Biomarker	HLA-D4
	HLA-DRB-1
Predictive Biomarker	Serum calprotectin
/Pronostic Biomarker	Survinin
	Anti savoie
	Antikeratin
Biomarkers for the Monitorization of the Disease Activity	CDAI (Clinical disease activity index).
	SDAI (Simple disease activity index)
	DAS 28 (Disease activity score)

Diagnostic Biomarkers:

Rheumatoid Factor: A rheumatoid factor is an essential diagnostic biomarker that identifies the presence of an autoantibody known as a rheumatoid factor against the Fc portion of IgG in the blood of a patient. Autoantibodies mistakenly attack the body's healthy cells and tissues, while normal antibodies fight off the antigen. These antibodies are directed against immunoglobulin (Ig) G's Fc region. IgM RF is the most routinely screened in clinical practice, while IgA and IgG RF are also available. About 80% of RA patients are detected with rheumatoid factor, and they might also be seen in a variety of other inflammatory disorders that cause prolonged antigenic stimulation, which limits their specificity [18]. RF positive increases the danger of RA, with higher titers indicating a higher risk [19].

Auto Antibodies against Citrullinated Proteins (ACPA): In studies on RA biomarkers, autoantibodies to citrullinated protein epitopes have received attention. Citrullination is a post-translational alteration of proteins that can result in the creation of novel epitopes which the immune system is not tolerant of and can result in the formation of new autoantibodies. The anti-cyclic citrullinated peptide (anti-CCP2) test, which has a very high diagnostic and prognostic value, is the most widely used ACPA. If more specificity is concerned, anti-CCP plays a vital role, but RF is also highly sensitive for diagnosing RA. Twenty to thirty percent of RA patients without RF have anti-CCP2 positivity. Besides erosive inflammatory arthritis, other rheumatologic conditions, including myositis and sjogren's syndrome, have also been linked to anti-CCP2 positivity.

Additionally, individuals with active pulmonary TB who only exhibit mild rheumatologic symptoms are anti-CCP2 positive. High titer RF antibodies and anti-CCP2 antibodies both enhance the risk of erosive joint damage, but anti-CCP2 antibodies are more dangerous. High titer anti-CCP2 antibodies are associated with a better clinical response to various biological products, which may enable clinicians to adjust treatment for the highest chance of response [20].

Erythrocyte Sedimentation Rate (ESR): The erythrocyte sedimentation rate is a test that measures indirect inflammation and determines the rate at which erythrocytes descend quickly when blood is suspended in a vertical tube. The results are expressed as millimeters of clear fluid (plasma) remaining at the upper portion of the tube after an hour. Various conditions, including systemic or local inflammatory processes, infection, malignancy, tissue damage, stage renal disease, nephrotic syndrome, and obesity, can cause elevated ESR readings. Women's ESR levels are somewhat higher than men's, increasing with age. Falsely low ESR readings can also result from several factors, including abnormal erythrocyte shape, severe leukocytosis, heart failure, and cachexia [21].

C-Reactive Protein (CRP): The C-reactive protein (CRP) test quantifies the level of CRP in blood. A protein called CRP is associated with inflammation in the human body. CRP is a member of the pentraxin protein family and is a pattern recognition molecule involved in the innate immune response [22]. Low-grade CRP increases have been linked to a number of metabolic stresses, such as atherosclerosis, overweight, type II diabetes, unhealthy lifestyles, poor diets, *etc.* [23].

An excess of pro-inflammatory cytokines in the RA synovium enhances the liver's production of the c-reactive protein. Hence it has been considered as a good choice of a biomarker [24]. (Elevated ESR and

CRP readings are part of the 2010 ACR/EULAR Classification Criteria for RA [25, 20].

Antinuclear Antibody (ANA): Antinuclear antibody (ANA) tests detect antinuclear antibodies in the blood, which fight with own body's tissues. The antibodies attach to a cell's nucleus. Many persons without RA, particularly women over 65, test positive for ANA. Other blood tests, such as anti-CCP, can help narrow down if you have RA. ANA tests look for both rheumatic and non-rheumatic disorders, such as autoimmune liver diseases. A rheumatologist will contact you if you have a positive ANA test to discover which has auto antibodies [27].

Multi-Biomarker Disease Activity (MBDA): A very important and widely used commercially accessible assay is the MBDA test. This assay uses an algorithm to indicate inflammation status in RA and summarizes the data into a single score after evaluating almost 12 serum protein biomarkers. The serum protein biomarkers are identified as epidermal growth factor (EGF), resistin, vascular endothelial growth factor A (VEGF-A), interleukin 6 (IL-6), tumor necrosis factor receptor type 1 (TNF-R1), matrix metalloproteinase-1 (MMP-1), VCAM-1, human cartilage glycoprotein 39 (YKL-40), serum amyloid (SAA), leptin, matrix metalloproteinase-3 (MMP-3) and CRP [20].

The MBDA test has been demonstrated to be a significant independent predictor of radiographic advancement at one year in experiment [26] and high baseline MBDA scores are a powerful independent predictor of radiographic advancement according to to post hoc analysis of the data [28]. In both cases, more research is required. This test is not currently recommended in the 2015 ACR Guideline for the Treatment of Arthritis. The cost-effectiveness of this test and its use in ordinary clinical practice are still debatable [20].

Investigational Biomarkers:

Anti–CARP: Anti-CarP, which is nothing but antibodies to carbamylated proteins, has been discovered in RA patient's blood. But unfortunately, studies could not show increased sensitivity or specificity compared to the RF and anti-CCP2 testing in current clinical practice [29]. When the enzyme peptidyl-arginine deiminase (PAD) converts the amino acid arginine to the amino acid citrulline, anti-carbamylated protein antibodies identify proteins [49].

Serum 14-3-3 ETA: An intracellular chaperonin protein called Serum 14-3-3etahas been explored as a diagnostic biomarker in RA. However, the evidence so far is insufficient to justify its routine clinical usage. When combined with RF and anti-CCP2, testing can enhance diagnostic rates (from 72 percent to 78 percent) or reclassify previously seronegative people. [30]. Further study is needed in this regard. Serum 14-3-3eta proteins are a family of molecular chaperones that play an important role in controlling intracellular activities, including proliferation, differentiation and metabolism. The 14-3-3 family of intracellular chaperone proteins has seven isoforms. In synovial fluid and serum samples from individuals with inflammatory joint disorders, only two isoforms, eta and y, are easily identifiable [31]. demonstrated that a novel soluble biomarker, 14-3-3," was present at significantly higher levels in synovial fluid and serum samples of patients with joint inflammation compared to healthy subjects, based on immunoblot analysis. However, more clinical data were needed to confirm the value of using this novel biomarker [32].

Anti-Mutated Citrullinated Vimentin (Anti-MCV): Genetically modified citrullinated vimentin (anti-MCV) assay is the newest member of the ACPAs family of assays. An isoform of vimentin called the anti-MCV antibody has arginine residues instead of glycine. Anti-MCV antibodies can also be present in anti-CCP- and RF-negative individuals, making them suitable candidates for diagnostic testing. When combined with RF and anti-CCP testing, anti-MCV antibodies can enhance the chance that nonspecific-undifferentiated arthritic patients will be diagnosed. There is no published information on the diagnostic value of anti-MCV testing in children and adults with arthritis who have already had positive results from RF and anti-CCP tests. So, few experts advise patients who test negative for one or both anti-CCP and/or RF tests to test for anti-MCV [50].

Serum COMP: COMP (cartilage oligomeric matrix protein) is a cartilage-derived marker of cartilage degradation that is considered as a prognostic factor in early RA [33]. Patients with knee

osteoarthritis (OA) and early rheumatoid arthritis have been shown to have higher levels of COMP fragments in their blood [34]. As a result, it has been proposed that patients with high levels of COMP in their serum may have accelerated articular cartilage deterioration. Patients with higher serum COMP levels had a quicker development of their disease [35].

Urine CTX-I AND CTX-II: The CTx-II biomarker has been extensively studied to assess cartilage turnover in patients with osteoarthritis and rheumatoid arthritis. The potential that CTx-II release is a partial reflection of bone turnover rather than a particular marker of cartilage turnover has been considered in recent papers. Because CTx-II is so widely utilized, it was evident that its cartilage specificity needed to be re-evaluated. Depletion of the epitopes from urine and affinity purification of the epitopes were used to evaluate ELISA specificity for CTx-I and CTx-II. The release of CTx-I and CTx-II from bone and cartilage was examined using cathepsin K or matrix metalloproteinases to digest cartilage and bone, and the release of CTx-I and CTx-II was measured using an ELISA. We also looked at the release of CTx-I and CTx-II in explant cultures from bone induced by osteoclasts and pro-inflammatory cytokine-stimulated cartilage explant cultures. Because CTx-II measures cartilage deterioration rather than bone turnover, it is a reliable biomarker of cartilage breakdown rather than bone turnover [36].

Serum Hyaluronan: Hyaluronan (HYA) is a linear extracellular polysaccharide in all tissues and bodily fluids, with the largest amounts in loose connective tissue [37]. It's found in synovial fluid, responsible for the fluid's distinctive rheological qualities, and cartilage, responsible for the backbone of proteoglycan aggregates and synovial tissue and joint capsule. In joints, serum hyaluronan work for lubrication, cartilage growth and bone growth, and inflammation reduction.

Hyaluronan is a connective tissue polysaccharide that has also been found in blood serum in concentrations < 100 micrograms/L (average 30-40 micrograms/L in middle-aged persons [37].

Serum MMP-1 AND MMP-3: Matrix metalloproteinases, MMPs, such as MMP-3 (stromelysin-1) and MMP-1 (collagenase-1), have been examined to see if they might predict the course of RA in terms of joint destruction. MMPs are the cartilage degrading enzyme. Early research failed to find a link between MMP-3 and MMP-1 levels in the blood and the course of RA in terms of joint destruction due to their performed study design. In early untreated RA, baseline serum MMP-1 and MMP-3 levels predict functional and radiographic prognosis and correlate with disease activity [38].

Genetic Biomarker:

HLA-DR4: HLA-DR4 The existence of the individual genetic component HLA-DR4 is related to the development of seropositive, but not seronegative, rheumatoid arthritis. These findings suggest that HLA genes play a crucial role in the etiopathogenesis of rheumatoid arthritis, most likely by creating a 'prearthritic' immunological environment on which the triggering events can develop [39].

HLA-DRB-1: HLA-DRB-1- The well-studied genetic component in RA is the shared epitope (SE), a set of HLA-DRB1 alleles with comparable amino acid sequences. Several investigations have discovered a link between SE and illness severity. It has been revealed that HLADRB1*0401 and DRB1*0404 are independent predictors of radiographic erosions. The Behandel Strategies (BeSt) study found no significant connection between HLA-DRB1 and radiographic progression in individuals with early RA treated with a strict control approach.[40]

Prognostic Biomarker:

Serum Calprotectin: Serum calprotectin is a type of calcium-binding protein that is mostly present in leukocytes and can be found in monocytes and macrophages. Many inflammatory disorders can raise the levels of calprotectin. As a damage-associated molecular pattern (DAMP) protein, calprotectin (S100A8/S100A9 protein) mostly reflects neutrophil activity. In inflammatory rheumatic disorders, serum calprotectin levels may be a useful substitute for acute-phase protein as a biomarker. S100A8 and S100A9, two non-covalently linked calcium-binding proteins, combine to form calprotectin, a heterodimeric

complex. They are a part of the 25-member S100 proteins family.

These two proteins are sometimes called calgranulin A and B or myeloid-related protein (MRP) 8 and 14. The cytoplasm of granulocytes has a high concentration of calprotectin (40–60% of the cytosolic protein total). It controls calcium homeostasis inside the cells, interacts with the cytoskeleton and microtubules, and participates in the intracellular movement of phagocytes. Calprotectin levels in normal serum are expected to range between 0.1 and 1.6 g/ml, and they can rise in various diseases such as infection, inflammation, or malignancy [41].

Survinin: Survivin, a tumor biomarker that belongs to the family of apoptosis inhibitors, has been found in RA patients [42] and it aids in the creation of functional T-cell receptors and memory T-cell differentiation. Survivin is required to express major histocompatibility complex molecules and mature dendritic cells, both of which are critical in the genesis of RA [43].

Anti-Savoie: Anti-Savoie (Anti-Sa), an RA-specific autoantibody, is found in roughly 43% of RA patients but not in the sera of people with other autoimmune illnesses or healthy people. Furthermore, anti-Sa positivity was found in 27% of RF - negative RA patients. Anti-Sa has a specificity of 92 to 98 percent, whereas its sensitivity is at 40 percent. Anti-Sa positive has been linked to more active and destructive illness, hence the high specificity has significant predictive significance. As a result, anti-Sa might be useful in RA diagnosis and prognosis.[44]

Antikeratin: Antikeratin antibodies were also found in RA patients who were rheumatoid factor seronegative, proving that antikeratin antibodies lack rheumatoid factor action. These results imply that antikeratin antibodies are detected at RA diagnosis and that the presence of antikeratin antibodies may be a good indicator of RA development [45].

Biomarkers for the Monitorization of the Disease Activity:

Disease Activity SCORE (DAS 28): To measure disease activity in RA on a group and individual level in both clinical practice and clinical trials, the Disease Activity Score (DAS) and the DAS28 were developed. Swollen joints, painful joints, acute phase response, and general health are all factors included in the continuous RA disease activity measure known as the DAS/DAS28. The primary purpose for which the DAS-based EULAR response criteria were created was for use in clinical research [46, 62].

DAS-28 is calculated based on the number of sore and swollen joints, erythrocyte sedimentation rate (ESR), and overall health on a VAS scale (0-100 mm). Low disease activity is classified as 3.2 or less, moderate disease activity as 3.2 to 5.1 and severe disease activity as more than 5.1 on the continuous DAS-28 Scale, which ranges from 0 to 9.4. In DAS-28, 2.6 is a standard remission threshold value [48].

Simple Disease Activity Index (SDAI): In both research and clinical contexts, the Simplified Disease Activity Index for Rheumatoid Arthritis (SDAI) scoring system has been proven to be reliable. When evaluated with other measures, it has been demonstrated to have the best sensitivity and specificity for predicting a physician's choice to modify DMARD medication. The swollen joint count (SJC) and tender joint count (TJC) based on a 28-joint assessment, global patient assessment of disease activity (PGA visual analog scale (VAS) 0-10 cm), global physician assessment of disease activity (MDGA VAS 0-10 cm) and C-reactive protein (CRP in mg/dl) are the outcome parameters used to calculate the SDAI [46, 47].

$$SDAI = TJC + SJC + PGA + MDGA + CRP$$

Clinical Disease Activity Index (**CDAI):** The Clinical Disease Activity Index (CDAI) is a composite index for measuring disease activity that excludes acute-phase reactants. For determining disease activity, the CDAI is based on a simple addition of the number of swollen/tender joints (28 joints), combined with patient and physician assessments on the VAS (0–10 cm) Scale. The range of the CDAI is 0 to 76. Low disease activity is classified as 10 or less, moderate disease activity as 10 to 22 and severe disease activity as more than 22. In CDAI, less than 2.6 is a standard remission threshold value [47, 48].

$$CDAI = TJC + SJC + PDGA + EDGA$$

Where TJC is the Tender Joint Count, SJC is the Swollen Joint Count, PDGA is the Patient's Disease Global Assessment (VAS 0–10 cm) and EDGA is the Evaluator / Assessor's Disease Global Assessment (VAS 0–10 cm).

TABLE 2: SENSITIVITY AND SPECIFICITY OF DIFFERENT BIOMARKERS

Biomarkers	Sensitivity	Specificity	Reference
RF	68.5%	77.1%	51
ACPA	76.1%	92.4%	51
ESR	48.4%	69.1%	52
CRP	71.3%	55.9%	52
ANA	42%	85%	60
AnticarP	46.8%	91.95%	53
Serum 14 3 3 eta	100%	78.57%	54
Anti MCV	81%	95%	55
Serum COMP	68%	70%	56
Serum hyaluronan	82.5%	100%	57
Antikeratin	48%	93%	58
Serum calprotectin	57%	79%	41
Anti-Savoie(Anti-Sa)	36.6%	96.9%	59

CONCLUSION: RA is a progressive inflammatory disorder that primarily targets the synovial membrane of the joints and initiates its destruction via several antigen-antibody interactions and other biomarkers that have been identified till today. The antibodies especially form immune complexes in the joints, leading to the attraction of immune cells and secretion of chemokines and cytokines, which can further augment the immune response and contribute to chronic inflammation and bone destruction. Patients with fast-developing RA have yet to be identified by a single feature. Hence, the study of biomarkers has brought major perceptions in rheumatology. The presence of RF and anti-CCP antibodies, as well as high ESR and CRP values, predicts a poor prognosis.

The discovery of illness-specific biomarkers that may correlate more closely with the disease process and assist well in classifying patients in terms of prognosis and treatment response is an intriguing area of expanding research. Several biomarkers have been suggested, but further research is needed before they can be acclaimed for general clinical usage. It is believed that it will showcase a better understanding of the pathophysiology of RA and the development of a new drug molecule in the future. It delivers fascinating and extensive areas for further research, leaving scope to gain more knowledge about biomarkers, immune responses, drug discovery, and evaluation for RA and other inflammatory disorders.

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