Clinical utility of autoantibodies and biologic markers in rheumatoid arthritis

Genga EK, Adam Sheik M, Oyoo GO

Department of Clinical Medicine and Therapeutics, School of Medicine, College of Health Sciences, University of Nairobi, P O Box 19676-00202, Nairobi, Kenya

Corresponding author:
Dr EK Genga.
Email: eugenekalman@gmail.com

Abstract

Objective: To review the current and emerging auto-antibodies and biologic markers in rheumatoid arthritis.
Data source: Published original research work and reviews were searched in English related to pathophysiology, diagnosis and auto antibodies in rheumatoid arthritis.
Study design: Only articles that emphasis on auto antibodies.
Data extraction: Online and library searches done.
Data synthesis: Data added and summarized.
Conclusion: There is an emerging role of biomarkers as efficient diagnostic and prognostic markers of immunopathogenicity of rheumatoid arthritis. Early identification of patients with Rheumatoid Arthritis (RA) and, in particular, of those likely to assume a more rapidly destructive form of disease is important because of the possible benefit from early, aggressive intervention with disease-modifying agents. Increasing our understanding of molecular triggers and targets driving pathogenesis of rheumatoid arthritis is crucial. This will lead to development of a signature biomarker that can predict persons at risk of developing rheumatoid arthritis, RA patients at predisposed to joint damage and predicting therapy response. This will offer rheumatoid arthritis patients with a more personalized tailor medicine to improve diagnosis, treatment and disease outcomes in patients with rheumatoid arthritis.

Key words: Rheumatoid arthritis, Autoantibodies, Bio markers

Introduction

Patients with Rheumatoid Arthritis (RA) follow a variable disease course with regard to outcome measures such as functional status or radiological assessment of joint damage. Early identification of patients with RA and, in particular, those likely to assume a more rapidly destructive form of disease, is important because of the possible benefit from early, aggressive intervention with modifying agents. This realization has prompted the investigation and measurement of numerous biologic 'markers' in blood and markers under consideration are accessible in routine practice, many are in the stage of experimental evaluation and require access to specialized technology and customized reagents. A biomarker can be defined as a measurable indicator of either normal or pathogenic processes or pharmacological responses to therapeutic interventions[1]. Clinically, biomarkers are commonly used for diagnostic (disease identification) and prognostic (predicted outcome or progression) purposes.

Diagnostic biomarkers distinguish individuals with active disease from healthy individuals. Prognostic biomarkers stratify patients according to prognosis. In RA, they identify patients at risk for rapid disease progression or early radiologic damage. Prognostic biomarkers are present at disease onset and do not change with treatment. Biomarkers of treatment response detect early and subtle changes in disease activity and are modifiable by effective treatment. Biomarker levels should be very sensitive to spontaneous or treatment-induced changes in disease activity, increasing in response to a disease and decreasing in response to effective treatment.

Table 1: Summary of the biomarkers/antibodies and their role in rheumatoid arthritis

Biomarker/ Antibody	Role in rheumatoid arthritis
Rheumatoid factor	Diagnosis, staging, prognosis
Anti-cyclic citrullinated peptide	Diagnosis, staging, prognosis
Erythrocyte sedimentation rate	Diagnosis, staging, prognosis
C-reactive protein	Diagnosis, staging, prognosis
Proinflammatory cytokines (tumour necrosis factor (TNF), interleukin 1 (IL-1), and IL-6)	Predicts disease severity
Inflammatory cells (macrophages, T cell infiltrates, and lymphoid cells e.t.c)	Decreases in number in response to RA treatment
Matrix metalloproteinase 1 (MMP-1), MMP-3,)	Predict severe disease, indicators of disease activity, treatment response and radiographic progression
Tissue inhibitor of metalloproteinase 1 (TIMP-1	Predict severe disease and treatment outcome
cartilage olgometric matrix protein (COMP)	Prediction of severe disease
C-terminal peptides from type II collagen (CTX-II)	Disease severity (bone destruction), markers of collagen breakdown
Helical portion of type 2 collagen (HELIX-II)	Disease severity (bone destruction)
carboxyterminal telopeptide of type 1 collagen (ICTP)	Disease severity (bone destruction), radiographic progression
Bone sialoprotein	Disease severity (bone destruction)
Methotrexate polyglutamates (MTXPGs)	Monitoring patients on methotrexate
receptor activator for nuclear factor B ligand (RANKL)	marker of bone degradation

What makes biomarkers so hard to identify?

Dozens of potential biomarkers have been identified in RA, yet few are ready for clinical use. The potential reasons include the following:

(i) Genetic variations may alter the pathogenic activity of certain biomarkers, causing small concentrations to be highly pathogenic in some patients and large concentrations to be relatively benign in others, thereby clouding our ability to interpret them.

(ii) RA is a highly heterogeneous disease, and some biomarkers may play a more pathologically-dominant role in certain patients than in others[2]. Different biomarkers are also associated with different pathologic mechanisms (e.g. inflammation vs. cartilage degradation). This may be predominant at different stages of disease progression[2].

(iii) Biomarker levels in blood and other body fluids may not reflect levels in the microenvironment of the joint[3]. The rate at which various molecules (e.g., TNF, IL-6) leak from within the joint to systemic body fluids may vary between patients, or even from joint to joint within the same patient. While many biomarkers are active in joint destruction or other pathological mechanisms, the concentrations of some biomarkers may not reflect the degree of their contribution[2].

This topic will review those markers that are used in clinical practice as aides in the diagnosis of RA or for prognostic purpose in patients with already established disease. Other tests that are still investigational or are of historic interest are also discussed.

Diagnostic, staging and prognostication biomarkers

Among the many biologic markers that have assessed for usefulness in estimating disease activity and prognosis of rheumatoid arthritis, only a few have found a role in clinical practice. At present, the main clinically useful biologic markers in patients with RA are rheumatoid factors and antibodies to citrullinated peptides for both diagnosis and predication of prognosis.

Rheumatoid factor

Rheumatoid Factors (RF) are autoantibodies directed against the FC portion of IgG. They are found in 75 to 80% of RA patients at some time during the course of their disease. As with any diagnostic test, however, the predictive value is also affected by the estimated likelihood of disease prior to ordering the test (ie, the pre-test probability). RF has a low positive predictive value if the test is ordered among patients with a low prevalence of RF-associated rheumatic disease or with few clinical features of systemic rheumatic disease. In a study of consecutive tests ordered by healthcare providers in a large academic medical center in the US, the prevalence of RA was approximately 13%[4]. The positive predictive value of RF (the likelihood of having disease if the

RF is positive) was only 24% for RA and 34% for any rheumatic disease. Thus, RF has a low positive predictive value if the test is ordered among patients with a low prevalence of RF-associated rheumatic disease or with few clinical features of systemic rheumatic disease. RF production may also occur in other diseases for example, some connective tissue diseases, such as Systemic Lupus Erythematosus (SLE) and primary Sjogren's syndrome. In addition, RF levels may be elevated in patients with malignancies (multiple myeloma) and certain infections such as HIV, malaria, rubella, hepatitis C, and following vaccinations.

Rheumatoid factor may have some prognostic value with regard to disease manifestations and activity. RF positive RA is associated with more aggressive joints disease, and is more commonly complicated by extra articular manifestations than sero-negative RA[5]. Studies have shown that rheumatoid nodules and vasculitis occur almost exclusively in seropositive patients and these findings are associated with increased mortality[6]. A case control study of 135 women with early RA found that patients with persistently positive RF had more erosions, nodules, extra articular disease and functional disability. They also noted that it was also associated with rapid radiographic progression and disease activity than sero-negative, or intermittently sero-negative individuals over a mean period of six years of follow up[7].

It has been noted that the presence of RF may antedate the clinical development of RA[8]. Population-based studies have shown that some healthy people with a positive Rheumatoid Factor (RF) develop RA over time, especially if more than one isotope is persistently elevated and if patients have high levels of RF[9, 10]. Retrospective study of stored blood samples collected as part of routine blood donation has demonstrated that nearly 30% of those who later develop RA have serum RF present for a year or more prior to diagnosis[11].

A Finish study of cohort of healthy individuals found that 9 of 129 subjects with positive sensitized sheep red blood cell agglutinations tests for rheumatoid factor subsequently developed seropositive RA over a 10 year investigation period, as compared to only 12 of 7000 subjects with negative test[6]. Thus, the presence of a positive sensitized sheep red blood cell agglutination test in a healthy individual is associated with a relative risk of approximately 40 for the development of RA. In the same study, however, 120 of 129 patients with positive RF did not develop RA over the 10 year period, demonstrating the lack of predictive value of the test.

Anti-Cyclic Citrullinated Peptide (CCP) antibodies

ELISA assays based upon either filaggrin derived from human skin or synthetic citrullinated peptides have high specificity and sensitivity for RA[12]. The target amino acid in filaggrin is citrulline, a post-translationally modified arginine residue. An ELISA assay that detects antibodies of cyclic citrullinated peptides. It has been reported to have a sensitivity and specificity of 47 to 76 and 90 to 96% for RA, respectively[13]. The sensitivity and specificity of anti-CCP antibodies for RA is dependent on the characteristics of the assay kit employed. The positive and negative values depend on both the assay and the study population. Higher values are reported with a later generations assay than with the origin[13]. What is the level of anti-CCP antibodies in normal people? They have been tested in ethnically diverse RA cohorts from North America, Europe, and Asia, and rates of anti-CCP detection are remarkably consistent. These studies used different controls, including healthy individuals and populations of various arthritic and non-arthritic inflammatory diseases.

The data has consistently shown that no control population has an equivalent rate of anti-CCP positivity to that found in RA, and the specificity remains high. This is despite having used controls with similar inflammatory disease processes. Early in the disease process, RA is often difficult to distinguish from other types of inflammatory arthritis and systemic inflammatory conditions, as their initial presentations may be similar. Several studies have examined the utility of anti-CCP antibody testing in distinguishing RA from other inflammatory diseases, by studying cohorts of patients who presented with non-specific early inflammatory arthritis. The ELISA for anti-CCP may be useful in the differential diagnosis of early polyarthritis. This was shown in a study on early arthritis study where 318 patients with undifferentiated inflammatory arthritis of less than 2 years duration were followed for 3 years[14]. Diagnosis of rheumatoid arthritis was made in 93% of those with an initial positive anti-CCP2 antibody test. In this study, anti-CCP antibodies conferred an odds ratio of 38.6 for the diagnosis of RA, compared to an odds ratio of 9.8 for rheumatoid factor.

A similar study on 524 patients with early undifferentiated arthritis of less than 2 years duration had anti-CCP antibody testing at inception. They were followed up longitudinally for 2 years[15]. After 2 years, 60% had self-limited inflammatory arthritis, 16% had persistent non-erosive arthritis, and 24% had persistent erosive arthritis. Anti-CCP positivity conferred an odds ratio of 4.58 for persistent vs. self-limited arthritis, as well as an odds ratio of 4.58 for erosive vs. non-erosive disease. Rheumatoid factor conferred an odds ratio of 2.99 for persistent vs. self-limited arthritis, and an odds ratio of 2.99 for erosive vs. non-erosive disease. Among patients with early oligo-or polyarthritis, anti-CCP testing appears to be predictive value in the 1gM-RF negative subgroup. This was illustrated by a prospective study that included 178 such patients[16] where they found that radiographic progression (More than 5 units by sharp score) was more frequent in the anti-CCP positive patient than those with negative test results (40 versus 5%, negative predictive value 95%). The anti-CCP test correctly predicted whether or not there would be worsening radiographic damage in 83% of these 1gM-RF negative patients. These findings were supported by similar data in studies of 282, 454 and 182 subjects[16].

Combination of anti-CCP antibodies and 1gM RF may be better for excluding the diagnosis of RA than

by testing for either antibody alone. Findings in respect to test performance from a study comparing the results of serologic testing in 196 patients with a clinical diagnosis of RA and 239 controls[13] were anti-CCP-sensitivity 56%, specificity 90%, 1gM RF – sensitivity 73 and specificity 82% and 1gM RF and anti-CCP – sensitivity 48 and specificity 96%. Patients with RA show considerable variability in disease activity, which can be difficult to predict at the onset of disease. Anti-CCP antibodies have proven useful in identifying those patients who are likely to have clinically significant disease activity. Some reports describe a decrease in titre of anti-CCP antibodies following successful treatment of RA. In a RA treatment trial, 35% of patients had a decrease in anti-CCP2 titres of 415%, while 19% had an increase of 415%; 46% of patients had anti-CCP2 titres within 15% of the baseline values. All but 5 of 242 patients with a positive anti-CCP2 antibody test remained positive when tested serially over a 3-year period[17]. In a similar study, serial anti-CCP2 levels were measured in 43 patients with RA who were treated for at least 2 years[18]. Mean anti-CCP2 titres at inception were 107_9.5 U, which fell to a mean of 92_9.8U (p¼0.0001) after 24 months of treatment. Titres were more likely to decrease in patients showing a greater degree of clinical improvement.

In addition to disease activity, irreversible damage from RA is an important outcome with significant impact on quality of life and functional capability. Predicting which patients will accrue damage is difficult, and disease activity parameters are not always accurate in predicting subsequent joint destruction. Anti-CCP antibody positive patients with early RA may be at increased risk of progressive joints damage. This was illustrated in a study of 145 such patients among whom there was more radiographically apparent damage after five years of observation in those with detectable anti-CCP antibodies than among the RF-positive patients[19]. The presence of anti-CCP antibodies was also predictive of more rapid radiographic progression in patients with early RA[20]. In a study addressing the progression of radiological damage in RA, anti-CCP1 antibodies were measured in 273 RA patients with <1 year of symptoms[21]. The patients were followed for at least 6 years and had plain radiographs of the hands and feet performed every 6 months. X-rays were graded by a radiologist blinded to the clinical data. After 6 years, anti-CCP1 positive patients had significantly more radiographic damage than anti- CCP1 negative patients ($p < 0.05$).

What is the role of anti-CCP antibody screening in rheumatoid arthritis? Ideally, screening healthy individuals at high risk of developing RA, for example those with a family history of RA, could allow for increased vigilance and the possibility of early intervention. As with RF, anti-CCP antibodies may be present prior to the appearance of symptoms of RA as shown in a case-control study of 79 patients with RA who had stored serum available from blood donations prior to the development of RA (1 to 51 samples per patient, dating up to 14.5 years prior onset of RA) 49% had detectable anti-CCP and/or anti-1gM RF on at least one occasion and 41% had anti-CCP detectable when symptoms first develop[22].

In another study of 59 patients with RA who had donated blood prior to the onset of disease, stored serum was analyzed for the presence of RF, anti-CCP, and for the HLA shared epitope. Of these three markers, anti-CCP was associated with the greatest risk of development of RA (odds ratio (OR) of 16, while 1gA RF and presence of the shared epitope were less powerful predictors (OR of 6.8 and 2.35, respectively). The combination of one or more HLA alleles for the shared epitope and anti-CCP antibodies was highly predictive of the subsequent development of RA; with an Odds ratio of 67[23]. Anti-CCP antibodies can appear years in advance of actual disease, and may eventually allow for identification of individuals who are likely to develop disease.

Erythrocyte sedimentation rate

The Erythrocyte Sedimentation Rate (ESR) determination is a simple and inexpensive laboratory test that is frequently ordered in clinical medicine. The test measures the distance that erythrocytes have fallen after one hour in a vertical column of anticoagulated blood under the influence of gravity. The rate at which erythrocyte fall through plasma, the ESR, depends largely upon the plasma concentration of fibrinogen[24]. ESR can be greatly influenced by the size, shape and number of red cells, as well as by other plasma constituents such as immunoglobulin. Thus, results may be imprecise and sometimes misleading.

Despite the shortcoming, an elevated ESR in patients with early RA is predictive of greater radiographic joints damage in subsequent years despite treatment with conventional disease modifying anti-rheumatic drugs[24]. ESR values tends to correlate with disease activity in rheumatoid arthritis and may be useful for monitoring therapeutic response[24]. ESR can aid in the diagnosis of RA, but it cannot be used solely for diagnosing RA. It is very useful when used with other parameters as outlined in the American College of Rheumatology guidelines, in the diagnosis and follow-up of RA patients. Wolfe and Michaud[25] showed that the ESR can be elevated when RA is quiescent clinically and vice versa. The authors concluded that the ESR role in the diagnosis and follow-up of RA patients may not be accurate.

C-reactive protein

C-reactive protein (CRP) has been advocated as an objective measure of disease activity in RA. Unlike the ESR, CRP can be measured using stored serum samples, is independent of the haemoglobin concentration, and can be performed in automated serum analyzer. Radiologic damage, as assessed by erosion counts in RA, is significantly more likely to progress when CRP and ESR are elevated, irrespective of the presence or absence of RF, and irrespective of therapeutic intervention.

Elevation of both ESR and CRP together are stronger indicators of radiologic progression than CRP alone[27]. In one study of 147 patients, for example,

absence or progression of radiologic joint damage after two years was correctly predicted in 83% of the patients using a combination of disease activity at presentation, (assessed by ESR, CRP or disease activity score) DR status and RF positivity[27].

However, a wide variation in the relationship between the degree of radiographic change and cumulative CRP was noted between patients, particulary those with low CRP levels. This inter-individual variability could not be accounted for by HLA DR4, positive RF, sex, or age and limits the value of serial measurement of acute phase protein in predicting radiologic progression.

Investigational bio-markers for disease severity
Proinflammatory cytokines

Pro inflammatory cytokines such as Tumour Necrosis Factor (TNF), interleukin 1 (IL-1), and IL-6 have been studied as surrogate markers for disease activity and inflammation in RA[28]. In early RA, a characteristic mix of cells and cytokines work together within the inflamed synovium to degrade cartilage and bone. Over time, this destructive activity typically manifests as RA. Ideally, it would be beneficial for rheumatologists to detect wayward cells and cytokines in patients with subclinical RA prior to symptom onset, or even in those who are only at risk for developing the disease[29]. The challenge is discerning a clinically relevant signal from biological background noise associated with normal physiological variations in cytokine levels. Inflamed synovium is thought to be the principal source of plasma IL-6 in RA, since IL-6 is often detected in high concentration in the synovial fluid. Thus, it has been postulated that plasma IL-6 concentration might reflect joint inflammation better than acute phase protein levels. A major stumbling block with Interleukin -6 (IL-6) is that it lacks specificity because it also has a major stimulatory effect on hepatic synthesis of acute phase protein. For example, serum IL-6 levels can vary up to 100-fold between individuals, increase with physical exertion, and change depending upon the time of day[29]. There is evidence to support its regulatory role in platelets production and etiopathologic role in the anaemia of chronic disease

Inflammatory cells

Researchers have studied various synovial cell populations harvested from joint biopsies in an effort to detect potential biomarkers of early joint damage. Within the heterogeneous cellular infiltrate, promising biomarkers include macrophages, T cell infiltrates, and lymphoid cells[32]. A promising marker of disease activity appears to be a certain type of macrophage—Sub-lining CD68+ macrophages that decreases in number in response to RA treatment[33]. Other potential synovial biomarkers have yet to be validated as biomarkers in RA. However the major stumbling block about these markers is how they can be tested on reliability and consistency. Even if more reliable markers are identified within the synovium, arthroscopic biopsies are regarded as an invasive technique and are unlikely to be used regularly in clinical practice[28].

Markers of joint damage or destruction

Although inflammatory markers provide important diagnostic and prognostic information in RA, they lack specificity to RA disease activity. For monitoring disease activity in rheumatoid arthritis biomarkers that reflect turnover in the synovium, cartilage, and bone may be more useful. Candidate biomarkers include matrix metalloproteinases (MMP), which are enzymes involved in articular cartilage degradation; urinary carboxyterminal crosslinking telopeptides of type I (CTX-I) and type II (CTX-II) collagen levels, which are markers of collagen breakdown; and receptor activator for nuclear factor B ligand (RANKL), a marker of bone degradation[28].

As part of the SPECTRA phase II clinical trial, researchers evaluated a panel of 22 biomarkers as potential indicators of disease activity, treatment response, and radiographic progression[38]. Among the markers of joint damage, matrix metalloproteinase 1 (MMP-1), MMP-3, and tissue inhibitor of metalloproteinase 1 (TIMP-1) showed the most promise. Both MMP-1 and TIMP-1 were significantly associated with radiographic progression, and early TIMP-1 activity following treatment onset predicted later therapeutic outcome[37].

Matrix metalloproteinase can degrade collagen and contribute to cartilage and bone destruction in RA. Genetics has been shown to play a major role as carriage of a polymorphism in the promoter region of the gene for matrix metalloproteinase 3 (MMp3) may be associated with more severe disease. This was illustrated in one study of 102 patients with early RA[37]. Homozygous carriage of particular polymorphism in the promoter region of the MMp3 gene (6A/6A) was associated with the presence of more progression of joint erosion and joint space narrowing than carriage of one or more alleles of a different type (5A).

The synovium is thought to be a dominant source hyaluronan, a marker that is strikingly elevated in the serum of patients with RA. *In vitro* studies demonstrates that synovial lining cell of rheumatoid joints produce detectable amount of hyaluronan, while lining cells on normal joints do not. Despite a short half-life of lining cells of 15 minutes, serum hyaluronan concentration has been found to correlate with disease activity[38]. One prospective study has suggested that, in early RA, serum hyaluronan may reflect ongoing joint destruction, and may even predict subsequent joint damage[39]. However, elevated serum levels of hyaluronan can be non-specific since they may vary with physical activity independent of the degree of synovitis.

Other markers that may be predominantly released from the synovium are matrix metalloproteinase l and 3 (MMP- 1 and MMP-3), enzymes that fragment matrix collagen. Elevated levels of MMP-3 and/or MMP-1 may correlate with increased radiographic joint damage[40].

Markers of cartilage metabolism may have some prognostic value in patients with RA. In early RA it has been shown that high serum level of cartilage olgometric

matrix protein (COMP), a member of the thrombospondin protein family can predict severe disease characterized by subsequent large and small joint destruction[41]. The same study that measured serum level of COMP in patients with RA, also measured serum levels of a putative markers of cartilage aggrecan synthesis, epitope 846, located on the chondroitin sulphate rich area of the aggrecan molecule. The epitope 846 levels were found to be elevated only in a group of patients with slow joint destruction, as compared with a group matched for age, gender and disease duration but with more destructive joint disease[42]. These data indicate the presence of cartilage reparative processes in the group with a more benign course, and suggest that elevated 846 epitope is indicative of a more favorable prognosis.

The aggrecan content of synovial fluid may also predict joint destruction. The chondroitin sulphate rich region of aggrecan is most abundantly detected in synovial fluids recovered from joints with little radiologic evidence of destruction, whereas the hyaluronan binding region of core protein is released in more severely damaged joints[42]. Measurement of cross-linked C-terminal peptides from type II collagen (CTX-II) in urine provide some prognostic information. A correlation between the excretion of these peptides and radiographic progression up to five-years in patients with early RA has been noted[43]. Similarly, urinary excretion of peptide derived from the helical portion of type 2 collagen (HELIX-II), also correlates with radiographic progression and is independent of other variables, including baseline CRP levels, joint damage, and urinary CTX-II excretion[44]. Findings of a study on rheumatoid arthritis patients revealed increased levels of both HELIX-II and CTV-II correlated with the highest risk of radiographic progression compared to those without an elevation of either of these markers.

As with cartilage, several bone specific markers are available and may have a useful purpose in patients with RA. Bone degradation can be assessed by detection of pyridinoline cross-links in urine. The pyridinoline levels have been found to correlate with disease activity in RA and diminishes after treatment with pulsed glucocorticoids and DMARDS[45].

Immunoassays are now available for measurement of other serum markers for bone collagen degradation like carboxyterminal telopeptide of type 1 collagen (ICTP). A three year follow up study in RA patients found elevated levels of serum ICTP compared to healthy controls. Throughout the follow-up, serum ICTP levels correlated with inflammatory parameters, and from the first year on, with the radiologic changes assessed annually. Initial ICTP levels correlated better than the other variables of disease activity with the subsequent erosive progression of joints, suggesting that its measurement may serve as a prognostic marker for joint damage in early RA[46]. A subsequent study found that ICTP levels in synovial fluid correlated better with prognosis than serum levels[47]. Bone sialoprotein is an osteoblast-derived protein preferentially expressed in juxtaarticular bone. Bone sialoprotein levels in synovial fluid correlate with joint destruction in both RA and osteoarthritis[48].

Investigational markers for treatment monitoring

Given the complications of the disease, high costs and potential safety risks associated with multiple courses of ineffective therapy, it would be highly preferable to be able to refer to a treatment algorithm that uses biomarkers of treatment response to assign patients to the type of therapy most likely to promote early disease control. The identification of biomarkers that would predict disease response would have an enormous impact on outcome. Unfortunately, research on predictors of treatment response in RA is still young so any major breakthroughs appears to be well down the road. We discuss some bio markers that have shown promise for treatment monitoring.

Bio-markers to methotrexate therapy

Treatment of newly-diagnosed RA often begins with methotrexate (MTX), followed by the switch to or addition of another DMARD or biologic agent in those who fail MTX monotherapy. As patients progress through treatment options, many will try multiple agents before finding the right combination that adequately controls their RA. Approximately 30% of patients with RA who begin MTX treatment discontinue its use within 2 years due to side effects or lack of efficacy[49]. As a prodrug, MTX requires enzymatic conversion to MTX polyglutamates (MTXPGs) to exert anti-inflammatory activity within the joints. However, several Single Nucleotide Polymorphisms (SNP) involved in MTX absorption and metabolism have the potential to interfere with the therapeutic effect of MTX[50]. One commercially-available assay measures MTXPG metabolites to determine whether partial or non-responders to MTX might benefit from continued dose escalation or require a change in therapy[51].

Role of genetic factors in monitoring treatment

Five anti-TNF agents are currently available for the treatment of RA— infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol. Large-scale studies evaluating treatment response to TNF inhibition are only available for infliximab, adalimumab, and etanercept. Although the therapeutic utility of TNF blockade is well established, approximately one-third of patients with RA have minimal or no response to anti-TNF therapy[52, 53]. Potential markers of treatment response may include single nucleotide polymorphisms in genes known to be involved in RA pathogenesis, genes encoding TNF receptors, or genes implicated in TNF metabolism. The –308G A/G polymorphism has emerged as a significant predictor of response to anti-TNF treatment. In a meta-analysis of 311 patients with RA, those who carried the A allele had a poorer response to anti-TNF therapy than those with the G allele[54]. In a study of patients treated with infliximab, those with the GG genotype were twice

as likely to respond to treatment as those with the AG or AA genotype[55]. The predictive value of the –308G A/G polymorphism has also been validated in trials of etanercept and adalimumab[56, 57].

Approximately one-third of patients do not respond to treatment with tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, suggesting the presence of a distinct subset of nonresponders[58]. SNPs for IL-6 influence the amount of IL-6 produced in response to various conditions and may influence the potential for response to anti- IL-6 therapy. For example, the -174 C/G polymorphism of the IL-6 gene significantly influences the amount of IL-6 produced in response to IL-1 and other inflammatory stimuli. The C allele, which is present in approximately 40% of individuals, is associated with significantly lower levels of plasma IL-6[59]. In patients with unusually low IL-6 concentrations, an IL-6 inhibitor may have little therapeutic benefit. An assay for the -174 C/G polymorphism may help to identify candidates who are more likely to benefit from anti-IL-6 therapy[60].

Conclusion

This paper outlines the auto antibodies and biologic markers used in the diagnosis and management of rheumatoid arthritis. There is an emerging role of biomarkers as efficient diagnostic and prognostic markers of immunopathogenicity of rheumatoid arthritis. They have been incorporated into various rheumatoid arthritis diagnostic and prognostic tools. These include DAS, ACR, EULAR, Simplified (SDAI) or Clinical (CDAI) Disease Activity Index criteria to assess disease activity and therefore treatment outcomes. Each method involves all or a combination of joint evaluation to varying degrees, and laboratory analysis of acute phase proteins such as Erythrocyte Sedimentation Rate (ESR) or C - reactive protein (CRP), and patient/physician subjective measures for disease activity or pain. This offers clinicians potentially reliable and objective tools in monitoring treatment of these patients. Early identification of patients with Rheumatoid Arthritis (RA) and, in particular, of those likely to assume a more rapidly destructive form of disease is important because of the possible benefit from early, aggressive intervention with disease-modifying agents. This realization has prompted the investigation and measurement of numerous biologic "markers" in blood and joint fluids that may serve as indicators of prognosis and the response to therapy. Although some of the markers under consideration are accessible in routine practice, many are in the stage of experimental evaluation and require access to specialized technology and customized reagents. Increasing our understanding of molecular triggers and targets driving pathogenesis of rheumatoid arthritis is crucial. This will lead to development of a signature biomarker that can predict persons at risk of developing rheumatoid arthritis, RA patients are predisposed to joint damage and predicting therapy response. This will offer rheumatoid arthritis patients with a more personalized tailor medicine to improve diagnosis, treatment and disease outcomes in patients with rheumatoid arthritis.

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