The potential roles for novel biomarkers in rheumatoid arthritis assessment

P.J. Mease

ABSTRACT
Comprehensive management of rheumatoid arthritis (RA) requires regular monitoring of disease activity, functional status, and structural damage to facilitate optimal patient outcomes. Tight control strategies have been successfully used in other diseases including diabetes and hypertension. Tight control requires frequent disease activity measurements in order to tailor treatment for individual patients, resulting in improved patient outcomes.

Current monitoring measures used in clinical practice are largely driven by subjective evaluation of signs and symptoms, which are critical but limited by assessor variability and may not reflect true biological change in a timely manner. Research suggests that novel biomarkers may provide quantitative, objective assessments of disease activity and structural damage risk in RA, which are not captured by current measures. The simultaneous use of multiple biomarkers in a single test algorithm may provide a more comprehensive quantitative representation of the overall complex heterogeneous biology of RA. This article reviews the current management strategies for monitoring RA and the potential impact that multi-biomarker assays may have on RA assessment, which may further improve clinical outcomes.

Introduction
Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease, with 1% to 2% worldwide prevalence (1). Although the incidence of RA varies geographically, the hallmarks of this progressive disease are the same for all patients – inflammation, joint pain, and bone and cartilage destruction that can lead to functional disability (2). The last decade witnessed significant advances in the treatment of RA, including improved treatment strategies and the introduction of new therapies, both traditional disease-modifying antirheumatic drugs (DMARDs) and biologic response modifiers that target key inflammatory mediators of inflammation (3-5). Despite these treatment advances however, many patients continue to experience chronic inflammation, progressive joint damage, and disability. Only modest improvements in survival rates have been observed for the first time in the last 40 years (6, 7).

In addition to better therapeutic agents, “tight control” or “treat to target” strategies for RA management bring an additional option for improving outcomes – one which is focused on more quantitative and frequent disease activity assessment. According to these new management strategies, RA care should include regular quantitative monitoring of disease activity, functional status, and structural damage to facilitate timely and appropriate changes in treatment, resulting in optimal patient outcomes (8).

The objectives of this review are to discuss the strengths and limitations of current assessment tools for these domains and to explore new paradigms. Specifically, this review will focus on biomarker-based assays and their potential to improve assessment of both disease activity and structural damage, which may thereby enhance clinical decision-making to improve patient outcomes.

Monitoring disease activity and structural damage in RA
Tight control strategies involve frequent disease activity measurements to tailor treatment decisions for individual patients with the goal of achieving a predefined level of remission or low disease activity (9, 10). Similar strategies have previously demonstrated improved patient outcomes in other disorders, such as diabetes (11, 12). In
RA, tight control approaches have been shown to improve patient outcomes in several clinical studies, including the FIN-RACo trial (13), the TiCoRA trial (14), the BeSt trial (15), and the CAMERA trial (16). These studies uniformly demonstrate that regular, quantitative disease activity measurements guiding aggressive treatment changes can improve clinical and radiologic outcomes.

Recently published guidelines from the European League Against Rheumatism (EULAR) (17), a joint international taskforce entitled Treat to Target (10) and a joint EULAR/American College of Rheumatology (ACR) Committee (18) recommend that, in addition to disease activity, physicians should also monitor structural damage, including joint space narrowing, and erosions. The EULAR/ACR collaborative guidelines for reporting disease activity in clinical trials also recommend that disease activity, function, and damage domains are all monitored (18). Detecting and treating the earliest signs of structural damage can prevent disability and significantly improve long-term patient outcomes (19-21). Since patterns and rates of structural damage vary throughout the course of a patient’s disease and do not always track with inflammation and clinical symptoms, monitoring skeletal damage in addition to disease activity remains critical for optimal management of RA.

Although disease activity and structural damage are linked, they are separable processes (22, 23). For example, erosions can continue even in the absence of clinical signs and symptoms when patients appear to be in clinical remission or low disease activity states. In a prospective study of 191 patients, Cohen et al. (24) analysed radiographs of hands, wrists, and feet, and found that 33% of RA patients in sustained remission at 3 and 5 years had a significant increase in radiographic damage between baseline and 5 years. Erosions were found in 36.7%, 53.3%, and 53.3% of patients in remission at baseline, 3 years, and 5 years, respectively. Other studies have also shown that despite the improvements obtained in clinical symptoms and inflammation with DMARD treatment, patients in clinical remission are still at risk for erosions (25, 26). Further evidence supports that the elevated inflammation associated with high disease activity states is not necessarily accompanied by severe erosive activity in all patients. For instance, patients without improvement of signs and symptoms on infliximab and methotrexate showed considerable benefit with regard to the joint destructive process, suggesting that inflammation and structural damage can be dissociated pathological processes (27).

**Current disease-monitoring tools for RA**

Clinical studies demonstrating improved outcomes with tight control typically used the Disease Activity Score 28 (DAS28) to measure disease activity. The DAS28 was developed and validated using a systematic process involving multiple independent studies (28). Although many RA clinical trials use the DAS28 to assess/measure disease activity, it has several limitations. First, several components of the DAS28, especially the swollen and tender joint counts and the patient global assessment, are subject to inter- and intra-observer variability (29-33). For example, a recent study of swollen joint counts confirmed that clinical inter- and intra-observer variability can be significant, and can have a substantial impact on the DAS28 score and consequently the management of patients (34). Second, calculation of a patient’s DAS28 score can be time-consuming and cumbersome, as evidenced by the nominal use of DAS28 in community practice in the United States (35, 36).

There are a number of clinical assessment tools for measuring disease activity in RA besides the DAS28. Newer disease activity indices, such as the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI), were validated based on their correlation to DAS28 (27, 37). The ACR Core Set can be used to determine the relative change in disease activity without determining the absolute level of disease activity, and is commonly used in clinical trials in the United States but (like the DAS28)

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions/Groups</th>
<th>n.</th>
<th>Medications at the start</th>
<th>Frequency of assessment</th>
<th>Disease duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIN-RACo (13)</td>
<td>Combination therapy*</td>
<td>97</td>
<td>SSZ, MTX, HCQ ± Predn</td>
<td>3 months (variable)</td>
<td>&lt;2 years</td>
</tr>
<tr>
<td></td>
<td>Monotherapy</td>
<td>98</td>
<td>SSZ ± Predn</td>
<td>3/6 months (clinical decision/ variable)</td>
<td>&lt;2 years</td>
</tr>
<tr>
<td>TICORA (14)</td>
<td>Intensive management*</td>
<td>55</td>
<td>DMARD, ia steroid</td>
<td>1 month (DAS)</td>
<td>&lt;5 years</td>
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<tr>
<td></td>
<td>Routine management</td>
<td>55</td>
<td>DMARD monotherapy</td>
<td>3 months (clinical decision)</td>
<td>&lt;5 years</td>
</tr>
<tr>
<td>BeSt (15)</td>
<td>Sequential monotherapy*</td>
<td>126</td>
<td>MTX</td>
<td>3 months (DAS44)</td>
<td>&lt;2 years</td>
</tr>
<tr>
<td></td>
<td>Step-up combination therapy*</td>
<td>121</td>
<td>MTX</td>
<td>3 months (DAS44)</td>
<td>&lt;2 years</td>
</tr>
<tr>
<td></td>
<td>Initial combination therapy + predn*</td>
<td>133</td>
<td>MTX, SSZ, predn</td>
<td>3 months (DAS44)</td>
<td>&lt;2 years</td>
</tr>
<tr>
<td></td>
<td>Initial combination therapy + infliximab*</td>
<td>128</td>
<td>MTX, infliximab</td>
<td>3 months (DAS44)</td>
<td>&lt;2 years</td>
</tr>
<tr>
<td>CAMERA (16)</td>
<td>Intensive strategy*</td>
<td>151</td>
<td>MTX</td>
<td>1 month (computer decision)</td>
<td>&lt;1 year</td>
</tr>
<tr>
<td></td>
<td>Conventional strategy*</td>
<td>148</td>
<td>MTX</td>
<td>3 months (clinical decision)</td>
<td>&lt;1 year</td>
</tr>
</tbody>
</table>

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is not often used in clinical practice (38). These tools (i.e. the SDAI, CDAI, and ACR Core Set) are also based on swollen and tender joint counts and patient or physician global assessments, so, while again valuable, they do not eliminate the variability inherent in the DAS28 (39-45).

Finally, patient-reported outcome measures, such as the Rheumatology Assessment Patient Index Data (RAPID), use selected components of the multidimensional Health Assessment Questionnaire and focus on the patient’s assessment of pain, fatigue, and functional status. These are critical assessments which guide care; however, they are also subjective and therefore inherently variable, both between patients and even within a patient, as the patient experiences the disease over time (36, 46).

Today, there are no validated laboratory tests that encompass the complex biological basis of RA. Standardised testing of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) allows quantitation of one aspect of RA disease activity. However, these are proteins associated with the acute phase response pathway. The pathophysiology driving RA inflammation is complex and heterogeneous, and CRP and ESR cannot capture the full complement of RA-specific disease processes, leading to challenges with their use across the broad RA patient population (47, 48). For example, one recent analysis of 1892 consecutive patients seen by 7 rheumatologists from Finland and the United States over 25 years demonstrated that ESR and CRP were normal at presentation in 35% to 45% of patients with RA (49).

Monitoring structural damage, meanwhile, relies on various imaging techniques, each with its own advantages and limitations (50). Radiography (x-rays and CT scans) are the conventional means of assessing structural damage and are readily available. However, relatively low sensitivity limits the monitoring frequency to once or twice a year at most, so that changes in skeletal progression due to disease alteration or treatment cannot be rapidly assessed. Furthermore, regular assessment using radiography in a chronic disease such as RA implies periodic, life-long exposure to radiation. Finally, as lagging indicators of damage, these techniques report established damage after the fact – often too late for prevention or mitigation. Magnetic resonance imaging and ultrasonography, while also lagging indicators of joint damage, are more sensitive than radiography and therefore exhibit less delay between the onset of erosive activity and evidence of damage on imaging. These modalities, however, require highly specialised expertise and expensive equipment (in the case of MRI), resulting in limited availability and significant inter- and intra-assessor variability.

Thus, better tools for measuring both disease activity and structural damage could complement existing approaches and facilitate more widespread use of “tight control” and “treat to target” strategies for chronic disease management in RA, with the ultimate goal of improving long-term patient outcomes. One promising approach that has garnered much attention recently is the use of biomarkers for evaluating RA disease activity and structural damage progression.

**Novel biomarker assays in other therapeutic areas**

Biomarker assays are fundamental to the diagnosis, monitoring, and treatment of many diseases, including various cancers, coronary artery disease, diabetes, and HIV (51-57). In addition to individual markers, in diseases with multi-factorial etiologies such as cancer and autoimmune diseases, multi-biomarker assays can simultaneously assess multiple disease pathways that may contribute to an individual patient’s disease. For example, a 21-gene RT-PCR assay (Oncotype DX®; Genomic Health, Inc., Redwood City, California) has been validated to predict recurrence risk and chemotherapy benefit in early-stage breast cancer (58).

Similarly, in the field of immune response, a 20-gene RT-PCR assay (AlloMap®, XDx Inc., Brisbane, California), which was validated to identify heart transplant recipients who are at low probability of rejecting their transplanted heart, has been incorporated in clinical practice and the International Society of Heart and Lung Transplant guidelines to minimise the need for (and risks associated with) periodic, invasive cardiac biopsies (59, 60).

Lastly, a novel serum-based, seven-biomarker test (PreDx Diabetes Risk Score model; Tethys Bioscience; Emeryville, California) has been validated to predict the risk of developing type 2 diabetes within a 5-year period (61). The PreDx model also outperformed additional measures such as haemoglobin A1c, fasting insulin, and a non-invasive clinical model including age, gender, BMI, waist circumference, and family history. The validation and adoption of these tests confirms the value of multi-biomarker approaches in complex, multi-faceted diseases.

**Novel biomarkers in RA – individual biomarker assays**

Rheumatoid arthritis is a complex, multi-factorial, and heterogeneous disease, with significant inter-patient variation in symptoms, natural history/disease course, and therapeutic response (62). Multiple cell types, tissues, and compartments are involved in RA pathophysiology, both within the affected joints and in the periphery (Fig. 1). The biological pathways primarily responsible for driving erosive activity and disease activity can vary from patient to patient and over time within a single patient (63). Studies have suggested different biological patterns in RA, from gene expression to synovial architecture, intrinsic (e.g. race, ethnicity, and gender) and extrinsic/environmental (e.g. diet and exercise) factors influence the contributions and interactions of different biological pathways – and ultimately the disease course – of RA in each individual (64-69).

For example, diffuse synovitis is seen more in patients with seronegative RA, while extra-articular spreading of RA with nodule formation is typically associated with granulomatous synovitis (70). Another study has shown that RA patients with synovial lymphocyte aggregates generally have a better response to tumour necrosis factor (TNF) inhibitor treatment (e.g. infliximab).
than those with only diffuse leukocyte infiltration (71). These studies and numerous others in the existing literature provide evidence of the heterogeneous nature of RA and suggest the existence of distinct pathogenic mechanisms that contribute to RA. Therefore, an understanding of the biological basis of disease activity and structural damage requires evaluation of the activity of multiple pathways.

Today, the only laboratory tests regularly used in the assessment of disease activity in RA are CRP and ESR (72-74), which are also utilised to calculate disease activity scores, such as the DAS28-ESR and the DAS28-CRP. However, as non-specific indicators of the peripheral response to inflammation rather than the processes driving RA pathophysiology, taken alone, these markers provide an incomplete picture of disease activity. Other biomarkers currently under investigation may capture additional components of the underlying biology of synovial inflammation and hyperplasia, cartilage degradation, and bone erosion (Fig. 1). For instance, multiple cytokines clearly contribute to RA, possibly differently in different patients, as evidenced by the success of cytokine-inhibiting therapies, such as TNF inhibitors, and IL-6 receptor antagonists in anti-TNF inadequate responders (75). Similarly, the vascular contribution to RA involves adhesion molecules, chemokines, and angiogenic factors (e.g., VEGF), while skeletal degradation appears to be driven by cytokines and matrix metalloproteinases (MMPs). The complexity of these biological interactions and their heterogeneity among patients suggest that multiple analytes may more accurately characterise the disease state (76, 77).

Indeed, numerous circulating biomarkers have been associated with disease activity in RA in individual studies, though none have yet gone through rigorous validation or been proven useful for clinical care (Table II). Serum amyloid A (SAA), for example, has been correlated with CRP (78). In a study of 185 patients with RA, SAA showed a greater incremental increase than CRP and was elevated in 40% of patients with normal CRP concentrations. These findings suggest that SAA may be a more sensitive marker of inflammation – and disease activity – than CRP. YKL-40, or human cartilage glycoprotein 39, is another often-studied marker, which is secreted primarily by chondrocytes and differentiated macrophages, and may promote chondrocyte and fibroblast proliferation and antagonise cartilage destruction (79-82). In a 1-year longitudinal study of 156 patients with RA, YKL-40 was increased in 54% of the patients with clinically active disease (83). Patients who changed from inactive to active disease after 12 months experienced an increase in serum YKL-40, while patients who changed from clinically active to inactive disease had

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Fig. 1. Distinct classes of molecules driving different types of interactions in RA.
B, B cells; DC, dendritic; FLS, fibroblast-like synovial cells; T, T cells.
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Markers of inflammation  
Erythrocyte sedimentation rate (ESR)  
C-reactive protein (CRP)  
Interleukin (IL)-1  
IL-6  
IL-8  
Serum amyloid A (SAA)  
Markers of destruction/destruction  
Metalloproteinases (e.g., MMP-3), cartilage oligomeric matrix protein (COMP)  
Synovial markers: urinary glucosyl-galactosyl pyridinoline  
Cartilage markers: carboxy-terminal crosslinking telopeptide (CTC) of type 2 collagen; aggrecan, hyaluronic acid  
Bone markers: CTC of type 1 collagen; pyridinoline crosslinks; bone sialoprotein; receptor activator for nuclear factor κβ ligand (RANKL), cartilage oligomeric matrix protein, urinary C-terminal cross linking telopeptide of type 1 collagen (CTX-I), CTX-II, and anticitrullinated protein antibodies (87-91).

Novel biomarkers in RA – multi-biomarker tests

Given the biological heterogeneity of RA, multi-biomarker tests have the potential to improve disease assessment. Rioja et al. (92) assessed 44 RA patients with proteomic arrays to determine a set of biomarkers which could distinguish between active and quiescent disease. Ninety-two analytes were assessed in plasma, resulting in 18 proteins which were statistically significantly up-regulated in active vs. quiescent RA (FDR ≤0.005). In multivariate modelling, a combination of 6 biomarkers showed promise in discriminating disease activity (IL-6, chemokine [C-X-C motif] ligand 13 [CXCL13], chemokine [C-C motif] ligand 23 [CCL23], transforming growth factor alpha, TNF receptor superfamily member 9, and macrophage colony-stimulating factor) with 91% predictive value for active vs. quiescent disease, moderately higher than that of IL-6 alone. Separately, Young-Min and et al. (93) assessed the contribution of novel biomarkers to predict radiographic progression in 118 subjects with early RA. Biomarkers including MMPs, urinary collagen markers, and COMP were assessed, along with traditional variables such as physician global assessment, swollen and tender joint counts, baseline Larsen Score and DAS28, by univariate analysis and by multivariate logistic regression. Both clinical variables and biomarkers were predictive at baseline and in an AUC-based longitudinal model in univariate analysis. A multivariate model containing MMP-3 and urinary CTX-II yielded statistically significant results (p<0.001) with an AUC of the ROC of 0.76; a model including these 2 biomarkers and swollen joint count had even greater performance, with AUC of the ROC=0.81 (using either a 44- or 28-swollen joint count). Studies to further validate these and other proposed biomarker combinations and to confirm benefit beyond existing measures, must be conducted in larger, independent cohorts of RA patients. More recently, a new test for RA disease activity, which includes 12 biomarkers (Vectra™ DA; Crescendo Bioscience; South San Francisco, California), has been developed and validated; this work also followed a stepwise process of biomarker discovery (94), algorithm development and finalisation (95), and final validation in an independent cohort (96). These types of multi-biomarker assays have the potential to provide rheumatologists with valuable, quantitative information on the individual disease biology of their patients.

As biomarker research evolves, it is important for clinicians to have a framework for assessing the clinical validity and clinical utility of novel assays. The Outcome Measures in Rheumatology Soluble Biomarkers Working Group of OMERACT has published draft guidelines on criteria for a single soluble biomarker of structural damage and includes measures of truth, discrimination, and feasibility (97, 98). Other groups have written on the optimal development and validation of multi-biomarker-based tests for diseases in general, including statistical methods and requirements for studies that now routinely explore correlations of tens, if not thousands, of biomarkers in a single

Table II. Selected potential biomarkers in RA.

| Genetic markers | Human leukocyte antigen (HLA)-D4  
| Autoantibodies | Rheumatoid factor (RF)  
| Markers of inflammation | Erythrocyte sedimentation rate (ESR)  
| Markers of destruction/destruction | Metalloproteinases (e.g., MMP-3), cartilage oligomeric matrix protein (COMP)  
| | Synovial markers: urinary glucosyl-galactosyl pyridinoline  
| | Cartilage markers: carboxy-terminal crosslinking telopeptide (CTC) of type 2 collagen; aggrecan, hyaluronic acid  
| | Bone markers: CTC of type 1 collagen; pyridinoline crosslinks; bone sialoprotein; receptor activator for nuclear factor κβ ligand (RANKL), cartilage oligomeric matrix protein, urinary C-terminal cross linking telopeptide of type 1 collagen (CTX-I), CTX-II, and anticitrullinated protein antibodies (87-91).  
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Several biomarkers have also been identified as potential indicators of structural damage in RA. For example, MMP-3 was assessed in a longitudinal study that followed 109 patients with recent-onset RA for 2 years (85). Regression analysis showed that serum MMP-3 levels at disease onset were statistically significantly up-regulated in plasma, resulting in 18 proteins which were statistically significantly up-regulated in active vs. quiescent RA (FDR ≤0.005). In multivariate modelling, a combination of 6 biomarkers showed promise in discriminating disease activity (IL-6, chemokine [C-X-C motif] ligand 13 [CXCL13], chemokine [C-C motif] ligand 23 [CCL23], transforming growth factor alpha, TNF receptor superfamily member 9, and macrophage colony-stimulating factor) with 91% predictive value for active vs. quiescent disease, moderately higher than that of IL-6 alone. Separately, Young-Min and et al. (93) assessed the contribution of novel biomarkers to predict radiographic progression in 118 subjects with early RA. Biomarkers including MMPs, urinary collagen markers, and COMP were assessed, along with traditional variables such as physician global assessment, swollen and tender joint counts, baseline Larsen Score and DAS28, by univariate analysis and by multivariate logistic regression. Both clinical variables and biomarkers were predictive at baseline and in an AUC-based longitudinal model in univariate analysis. A multivariate model containing MMP-3 and urinary CTX-II yielded statistically significant results (p<0.001) with an AUC of the ROC of 0.76; a model including these 2 biomarkers and swollen joint count had even greater performance, with AUC of the ROC=0.81 (using either a 44- or 28-swollen joint count). Studies to further validate these and other proposed biomarker combinations and to confirm benefit beyond existing measures, must be conducted in larger, independent cohorts of RA patients. More recently, a new test for RA disease activity, which includes 12 biomarkers (Vectra™ DA; Crescendo Bioscience; South San Francisco, California), has been developed and validated; this work also followed a stepwise process of biomarker discovery (94), algorithm development and finalisation (95), and final validation in an independent cohort (96). These types of multi-biomarker assays have the potential to provide rheumatologists with valuable, quantitative information on the individual disease biology of their patients.

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experiment (99, 100). In general, the authors of these publications agree that the development of biomarker assays requires the use of multiple, independent, sizable cohorts to both develop and validate a novel test, in order to reduce false discoveries and ensure that these new tests are reproducible across the relevant population. There is also general agreement that both analytical validity (accuracy and reproducibility) and clinical validity must be ensured.

Conclusion
Regular assessment of disease activity and structural damage is recommended by rheumatologists and guideline committees around the world. Tight control strategies employing regular measurement with resulting treatment changes designed to reach a specific disease activity goal have shown improvements in patient outcomes. Objective, precise, and easy-to-use measures which can standardise assessment of disease activity and skeletal damage progression in patients with RA have the potential to further improve patient outcomes. Extensive research is ongoing to better understand biomarkers that drive biological processes underlying disease activity and structural damage. Until now, individual biomarkers have not been shown to adequately capture the complexity and heterogeneity of RA and hence are not heavily relied upon in clinical practice. However, coordinated, quantitative measurement of multiple biomarkers associated with different aspects of the disease may encompass this heterogeneity. As shown in other disease states, such technology has the potential to complement existing measures and enable more consistent and easy-to-use measures which can translate to reduced rates of complications and improved quality of life for patients suffering from RA.

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