Optimizing Rheumatoid Arthritis Therapy: Using Objective Measures of Disease Activity to Guide Treatment

Gary M. Owens, MD

BACKGROUND: Rheumatoid arthritis (RA) affects approximately 1.5 million individuals in the United States, or approximately 1% of the US adult population. In women, RA most often begins between age 30 and 60 years; in men, it often starts later in life. Patients with RA may have rapid declines in physical function that can begin early in the disease course. Disability increases most rapidly during the early years of the disease course, and if patients are not accurately diagnosed and do not receive appropriate care early, substantial functional declines may result.

OBJECTIVE: To review strategies and clinical assessment tools that may optimize patient outcomes by using objective measures of disease activity.

DISCUSSION: The goal of treatment for patients newly diagnosed with RA should be preventing joint damage from developing by employing early and aggressive approaches to therapy that minimize disease activity. Likewise, for established disease, treatment should be aimed at limiting the progression of existing joint damage. Substantial advances have been made in the treatment of RA over the past 2 decades, in large part as a result of better understanding of the biology of RA and the resultant introduction of biologic therapies. In 2010, an international task force published recommendations for a treat-to-target management approach to RA, much of which was based on the use of biologic drugs. This treatment strategy emphasized that the primary target in the treatment of patients with RA should be clinical remission or low disease activity. The tools necessary to measure RA disease activity are often incomplete, imprecise, or rely on a combination of physician and patient subjective evaluations. There is no one symptom, laboratory measure, or clinical tool that provides a truly accurate assessment of disease activity in patients with RA.

CONCLUSION: Thus, there is a large gap between what is recommended in clinical guidelines and the actual practice of rheumatologists. Better methods of assessing RA disease activity are still needed to enable widespread adoption of guidelines in the clinical community.

KEY WORDS: rheumatoid arthritis, disease activity, objective measures, clinical assessment, disease-modifying antirheumatic drugs, treat-to-target approach, multibiomarker test

Rheumatoid arthritis (RA) is an inflammatory arthritis that has been formally described for more than 2 centuries in the medical literature. The first description of RA acknowledged by modern medicine appeared in the 1800 dissertation of Augustin Jacob Landré-Beauvais, in which he described the symptoms and signs of what we now call RA.1 There is pictorial evidence of the disease in European paintings dating back to 1631.2 However, the term *rheumatoid arthritis* did not emerge until 1859, when Alfred Garrod gave the disease its current name.3 His work differentiated arthritis from gout and also categorized RA as a distinct condition.4

After more than 2 centuries of work, we now understand more about the cellular biology of RA, but the underlying cause of the disease remains elusive. The leading hypothesis for what causes RA (and the majority of other autoimmune disorders) is that it results from a specific environmental exposure in a genetically susceptible individual.4 A better understanding of the pathophysiology of RA opened the door to therapeutic advances that include the development of traditional disease-modifying antirheumatic drugs (DMARDs), the use of DMARD combinations, and the creation of highly specific biologic DMARDs.

An increasing number of therapeutic interventions have become available. Contemporary treatment strategies that are based on early diagnosis, treating to target, and tight monitoring have helped patients with RA better achieve their treatment goals. However, RA still presents substantial management challenges for clinicians and for patients.

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KEY POINTS

- Rheumatoid arthritis (RA) affects approximately 1% of the US population and can result in substantial functional decline.
- Early intervention with disease-modifying antirheumatic drugs to attain remission or low disease activity has become the standard of care for the treat-to-target approach.
- To achieve this goal, clinicians require an accurate and objective method to measure disease activity.
- The current tools used to measure disease activity are incomplete, imprecise, or rely on subjective evaluation by patients or physicians.
- Such drawbacks have led to research on effective, easy-to-use methods that are practical for clinical settings.
- A blood test that combines multiple serobiomarkers into a single score may support the current clinical goals for treatment of patients with RA.
- Clinical studies of this method indicate that it may be useful for guiding therapy.

Epidemiology, Diagnosis, and Comorbidities

It is estimated that RA affects approximately 1.5 million individuals in the United States, or approximately 1% of the US adult population. RA is significantly more prevalent among women, with approximately 2.5 times as many women as men having the disease. The symptoms of RA may begin at any age. In women, the onset of disease is typically between age 30 and 60 years; in men, RA begins later in life. The disease is typically lifelong. The average age of a patient with RA is 67 years, making it a known. From a genetic standpoint, we know that first-degree relatives have double the risk for RA.7

The diagnosis of RA is made clinically, based primarily on the patient’s medical history and physical examination. Patients usually present with pain and stiffness in multiple joints, although 33% of patients initially experience symptoms in just 1 or a few joints. In the majority of patients, symptoms emerge gradually, taking weeks to months to evolve. Often, RA starts with 1 joint and is accompanied by prodromal symptoms of anorexia, weakness, or fatigue. In approximately 15% of patients, disease onset occurs more rapidly, over days to weeks. In 8% to 15% of patients, symptoms begin within a few days of a specific event, such as an infection.

RA is a systemic inflammatory condition that affects many organ systems, directly or indirectly, in addition to the musculoskeletal system. On average, the patient with established RA has 2 or more comorbid conditions. RA can be associated with various forms of cardiovascular disease, including pericarditis, cardiomyopathy or myocarditis, cardiac amyloidosis, coronary vasculitis, arrhythmias, valvular disease, and congestive heart failure. Ischemic heart disease and congestive heart failure are more common among patients with RA than in the general population, and are associated with an increased mortality rate. The risks for serious infection and lymphoma are also increased with RA.

Economic Burden

In addition to its serious clinical consequences, RA has important economic implications. The direct and indirect medical costs associated with RA are substantial, including costs for medications and ambulatory and office-based care, and costs associated with diminished quality of life and productivity. This economic burden is compounded by the large proportion of patients with RA who have associated cardiovascular disease and other comorbidities. It is difficult to gauge the precise cost of RA, and analyses of RA-associated costs have produced wide ranges of cost estimations.

Studies published between 2007 and 2012 have suggested that the annual direct medical costs per patient with RA range from $2000 to $10,000, with estimated indirect costs ranging from $1500 to $22,000. In a 2015 study, Curtis and colleagues used a claims-based algorithm to estimate the mean 1-year cost of a biologic drug for an effectively treated patient. They found that the cost for a biologic drug for RA was $43,935 for etanercept, $49,589 for golimumab, $52,752 for adalimumab, $62,300 for abatacept, and $101,402 for infliximab.

The economic burden of RA has grown substantially since the introduction of biologic therapies in the mid- to late-1990s. Many payers now report that the biologic drugs to treat RA are among the top 5 drug categories by total cost. Gleason and colleagues found that among all patients receiving treatment with a specialty drug in 2010, the annual costs of the specialty drugs accounted for more than 50% of the total medical cost for the individual patient. For patients with RA, the annual drug cost was $18,098 and accounted for 53% of the total medical and pharmacy cost ($34,163). Furthermore, the annual growth in per-patient per-year (PPPY) cost of care from 2008 to 2010 for patients with RA was 8%; the increase in specialty drug cost PPPY was calculated to be 5.6% during the same period.

Importance of Early Diagnosis and Treatment

Patients with RA may experience rapid declines in physical function that can begin early in the disease
Figure  Functional Decline Begins Early in Rheumatoid Arthritis∗

<table>
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<th>Years from symptom onset</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>Moderate loss of function</td>
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∗These data predate the introduction of biological drugs.  
†50% rates of loss of function based on HAQ scores.  
HAQ indicates health assessment questionnaire.  

course (Figure). Disability increases most rapidly during the early years of the disease course, and if patients are not accurately diagnosed and do not receive appropriate care early, substantial functional declines may result.19 There is a strong causal relationship between joint damage and subsequent disability. Although this disability is most marked in late RA, there appears to be a “threshold” effect with disability having a more linear relationship to damage when radiographic scores for total joint damage exceed 33% of the maximum possible score.20

Therapeutic strategies should be aimed at limiting joint damage early to improve long-term functional declines.21-26 The goal in the treatment of newly diagnosed patients should be to prevent joint damage by using early and aggressive approaches to therapy that minimize disease activity. Likewise, for established disease, treatment should be aimed at limiting the progression of existing joint damage. However, even though evidence-based guidelines recommend early and aggressive treatment of active RA,22 population-based studies of DMARDs in patients with RA continue to demonstrate suboptimal rates of actual DMARD use, ranging from only 30% to 71%.21-26

**Changing Treatment Approaches**

Substantial advances have been made in the treatment of RA during the past 2 decades, in large part as a result of better understanding of the biology of RA and the resultant introduction of biologic therapies. With these advances comes the expectation of improved clinical outcomes for patients with RA. Historically, the treatment of RA focused on symptom control and pain management, not on controlling disease activity or preventing disability. The treatment paradigm shifted between 1995 and 2005 with the introduction of several biologic agents. In 2010, an international task force published a series of recommendations for a treat-to-target management approach to RA, much of which was based on the use of biologics.27

This treatment strategy emphasized that the primary target for RA treatment should be clinical disease remission.26,27 For patients with long-standing or aggressive disease, low disease activity may be an acceptable alternative therapeutic objective. Until the desired outcome is attained, therapy should be adjusted as often as monthly in patients with high to moderate disease activity. Therapeutic adjustments should be made every 3 to 6 months in patients with sustained low disease activity or remission.27

This strategy was updated in 2013 with the European League Against Rheumatism recommendations for the management of RA, which also emphasized that treatment with DMARDs should begin as soon as the diagnosis of RA is established.28 Similarly, in the most recent guidelines for RA management issued by the American College of Rheumatology (ACR), remission or low disease activity is the stated goal of treatment for early RA (disease duration <6 months) as well as established RA.22

Critical to the treat-to-target strategy is the need for a standardized, periodic, and reliable assessment of disease activity over time.29 However, no standard measure of disease activity was established in the treat-to-target recommendations for the assessment of disease activity by the clinician.29 Rather, clinicians were left to choose an approach from a number of measurements, many of which are not routinely used in clinical practice.29

**Current Assessment Tools: Need for Improvement**

Many studies of RA show that treating to target improves outcomes.23,29,30 As healthcare reform in the United States accelerates, the requirement for an assessment of disease activity in patients with RA has become one of many national targets for quality measures. For example, the Physician Quality Reporting System, a pay-for-reporting program administered by the Centers for Medicare & Medicaid Services, includes a quality measure for assessing whether physicians measure RA disease activity using a standardized scale or a composite index. It also requires physicians to classify each patient’s RA disease activity as low, moderate, or high, at least annually. Yet the tools to support this assessment are often incomplete, imprecise, or rely on a combination of physician and patient subjective evaluations to measure disease activity. For patients with RA, there is no one symptom, laboratory measure, or clinical tool that provides a truly objective assessment of disease activity.

Lack of an objective disease activity measure is a major issue, because although current therapies have the potential to prevent joint damage and disease progression, they also carry significant toxicities. Therefore, se-
lecting the right treatment to achieve low disease activity while balancing potential side effects and toxicity is a major concern for clinicians. Because of the lack of consensus for using a single measure of disease activity, several composite tools have been adopted by clinicians. The first composite tool for measuring RA disease activity was developed in the 1950s; today, more than 60 such tools are available.

In 2012, the ACR convened a working group on disease activity assessment tools and published recommendations for clinically applicable measures of RA disease activity. After reviewing 63 existing tools for RA assessment, the ACR committee narrowed the list to 14 measures for further evaluation. Practicing rheumatologists rated 9 of these 14 measures as most useful and feasible. From these 9 measures, the ACR selected 6 assessment tools (see below) for inclusion in the final set of ACR-recommended measures for RA disease activity.

Realizing the heterogeneity of settings in which healthcare is delivered to patients with RA in the United States, the ACR working group selected the following 6 tools:

1. Patient-reported assessments
   a. Patient Activity Scale (PAS)
   b. PAS-II
   c. Routine Assessment of Patient Index Data (RAPID-3)
2. Composite physician and patient assessment
   a. Clinical Disease Activity Index (CDAI)
3. Composite measures with laboratory acute-phase reactants
   a. Simplified Disease Activity Index (SDAI)
   b. Disease Activity Score based on 28 joints (DAS28).

None of these measures is ideal. Patient-driven composite tools (PAS, PAS-II, RAPID-3) have the advantage of being relatively easy to use in clinical practice, because they do not require provider assessments such as formal joint counts. Patients can often complete these measures on standardized paper or electronic forms in the waiting room, making them very practical to use.

However, these patient-reported tools have drawbacks. Although their components have been found to be reliable, valid, and sensitive to change, long-term outcomes regarding joint damage assessed by these 3 measures (PAS, PAS-II, RAPID-3) have not been studied directly. Another major concern about these tools is their lack of a formal joint assessment—something that is thought to lend significant validity to a clinical measure of RA disease activity.

The CDAI, a patient and provider composite tool, includes 3 components of provider assessments—provider global assessment, 28 swollen joint count, and 28 tender joint count—and 1 patient-reported tool. However, the CDAI is relatively time-consuming, because it requires providers to perform extensive joint counts reliably and consistently. Similar to the patient-reported tools, although the components of CDAI are reliable, its overall reliability is not known.

The DAS28 is a composite tool that includes a laboratory measure of disease activity, and thus it has the additional advantage of an objective and quantifiable measurement. However, as with the other ACR-recommended assessment tools, there are some drawbacks, including a complex formula that cannot be calculated by hand. Specifically, the inclusion of acute-phase reactants adds complexity. The erythrocyte sedimentation rate (ESR) contributes a sizable portion (15%) of the information in the DAS28-ESR. Therefore, remission may be underestimated in high ESR states. Similarly, in low ESR states, remission criteria may be met but patients may still have a number of swollen joints.

Like the DAS28-ESR, the DAS28-CRP (which differs only by using C-reactive protein [CRP] rather than ESR) may also provide an incorrect estimate of remission, because it is generally lower than the DAS28-ESR. Another consideration is that newer biologic agents that target specific inflammatory cytokines are differentially reflected in the ESR and CRP, and, therefore, may disproportionately lower the DAS28-based composite score.

Based on the twin goals of measuring disease activity and achieving minimal or no disease activity, quantification of the level of RA disease activity is essential to guide therapy. Yet, despite considerable effort to promote the assessment of RA disease activity in a quantitative manner, the use of these measures in clinical practice is lagging.

In a 2005 survey of US rheumatologists, only 6% of respondents were using the DAS28 or a similar quantitative assessment measure. Thus, there is a large gap between what is recommended in clinical guidelines and the actual practice of rheumatologists. Better methods of assessing RA disease activity are still needed to enable widespread adoption of guidelines in the clinical community.

### Role of a Multibiomarker Disease Activity Test in Managing RA

As noted, there is an unmet need for an accurate, objective, and quantitative tool for measuring disease activity in patients with RA. Although the 6 ACR-recommended measures of disease activity can be used in clinical practice, they can only be of clinical value if they are used consistently. Simply put, rheumatologists have never had a single symptom, clinical measure, or laboratory test to objectively assess the severity of disease activity or the risk for future joint damage—either when initiating therapy or when evaluating the response to therapy.
Because the central focus of treat-to-target strategies is to achieve clinical remission or low disease activity, it is essential that physicians have a reliable and objective measure of disease activity.\textsuperscript{17-29} DMARDs (biologic and nonbiologic) have the potential to prevent joint damage and achieve the treat-to-target goals, but they may have serious adverse effects. Therefore, it is important that physicians assess the effect of treatment on disease activity so that, if a given therapy is ineffective, appropriate alternative treatments can be selected to reach treatment goals as soon as possible.

This need for better measures of RA disease activity is greater than ever, because current guidelines recommend that treatment be targeted to achieve remission and prevent joint damage.\textsuperscript{22} In addition, there is growing interest in personalizing treatment to minimize unnecessary therapy and control costs.

To address this unmet need, it was postulated that multiple serum biomarkers combined into a single score could accurately measure RA disease activity.\textsuperscript{37} After extensive assessment, Centola and colleagues at the Oklahoma Medicare Research Foundation developed a multibiomarker disease activity (MBDA) blood test that uses 12 biomarkers and a mathematical algorithm to generate a score between 1 and 100, which correlated with RA disease activity.\textsuperscript{17}

The MBDA panel includes cytokine-related molecules, adhesion molecules, growth factors, hormones, skeletal-related proteins, matrix metalloproteinases, and acute-phase reactants. Curtis and colleagues observed the relationship between the MBDA score and clinical disease activity, as measured by the DAS28-CRP tool, before and after 6 to 12 weeks of methotrexate therapy or a biologic therapy.\textsuperscript{38} They concluded that:\textsuperscript{38}

- The MBDA algorithm score correlated with the DAS28-CRP tool, with an area under the curve of 0.85 (\textit{P} < .001).
- Changes in the MBDA score after 6 to 12 weeks of treatment could discriminate ACR criteria for 50% improvement (\textit{P} = .03) and DAS28-CRP improvement responses (\textit{P} = .002).
- Among patients receiving treatment with methotrexate or with an anti–tumor necrosis factor biologic agent, the MBDA scores were significantly lower than baseline values at weeks 2, 6, and 12 (\textit{P} < .001), when all patients were analyzed together.

Other studies have confirmed the clinical validity of the MBDA score for assessing RA disease activity.\textsuperscript{39,40} Hirata and colleagues showed that the MBDA score correlated significantly with DAS28, SDAI, CDAI, and a measure of physical function, the Health Assessment Questionnaire Disability Index.\textsuperscript{41} In a clinical practice setting, the MBDA score was used in clinical practice.

Conclusion

There remains a significant unmet need for a simple, easy-to-use measure of RA disease activity that can be incorporated into clinical practice. Easier-to-use objective measures for disease activity in patients with RA are currently in development. Recent studies of an MBDA score, calculated from a blood test, support the clinical approach to provide tight control of patient therapy. This approach, furthermore, shows promise as a guide to RA therapy, because it has the potential to provide clinically valid data on disease activity, without depending on the physician or the patient assessments that are not routinely used in clinical practice.

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Author Disclosure Statement

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References


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Closing Gaps in Health Plan Performance with Stakeholder Collaboration

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EMPLOYERS/HEALTH PLANS: For most commercial health plans and employer-sponsored health plans, immunology represents a significant area of healthcare spending. Rheumatoid arthritis (RA) is a common condition within that category, and continues to grow as the population ages and medical technology advances. Despite the improvements in understanding the disease and its underlying pathophysiology, much remains unknown.

Treatment strategies have emerged that work well and can reduce healthcare costs and improve the population’s health. As Dr. Owens points out in his article,1 however, there are gaps in measuring RA and in the diagnostic tools available to assist clinicians in effectively managing the disease. In addition, clinicians embody a large gap between desired outcomes and real-world practice because they often do not follow clinical guideline recommendations. This dual set of gaps represents a challenge for purchasers of healthcare who increasingly seek year-over-year improvements in plan performance in both clinical and economic domains.

During the past several years, the National Employer Initiative on Biologic & Specialty Drugs has conducted an annual survey of employer plan sponsors that has shown a shift to a more balanced result in plan performance between economic and clinical parameters.2,3 The keys to achieving that result typically include the closing of gaps in plan execution, improving collaboration among healthcare providers, and ensuring consistency in the delivery of evidence-based medicine, including the appropriate use of biologic drugs.

Partnerships between multiple stakeholders are evolving in response to decreased reimbursement schemes that, in many cases, result in a need for drastic administrative expense reductions to offset income reductions. Collaborations, such as accountable care organizations, patient-centered medical homes, and various direct contracted relationships between healthcare vendors and employers, are demonstrating commercial health plan cost-savings that have the potential to benefit both the patient and the employer plan sponsor. Some of those collaborations also include shared or at-risk arrangements in the contracting strategy. Blue Cross Blue Shield plans, among others, have piloted and pioneered the expanded use of such contracts in a post-Affordable Care Act marketplace.

PATIENTS/PROVIDERS: Through shared risk arrangements, the use of more effective measures of performance by all stakeholders aids in driving the desired change in the healthcare delivery system. Today the purchasers of healthcare include patients, because they are now part of the shared risk equation through a variety of high-deductible health plans. Expect increased interest in the results from clinical measures of performance that may be tied to a rapid increase in the use of biologic drugs during the next few years.

The increased use of high-deductible health plans by consumers and shared risk among clinical providers still requires an approach that addresses the emotional needs of patients who are in treatment programs. Although better methods of assessing RA are needed, so is closing the treatment decision gap among providers. Patients need support with their treatment programs to achieve optimal performance from the purchaser’s healthcare investment. Encouraging providers to deliver evidence-based healthcare to actively engaged patients can result in economic success for all stakeholders.