Monitoring Response to Treatment in Rheumatoid Arthritis
Which Tool is Best Suited for Routine “Real World” Care?

Yusuf Yazici, M.D.

Abstract
Rheumatoid arthritis treatment is a fast changing and advancing area. Current drugs are now better utilized and new medications continue to be developed. The main challenge is to identify which patients are responding to treatment and to objectively quantify their response or nonresponse. There is a need for more rheumatologists to pursue use of an objective assessment tool in routine clinical care. Therefore, knowledge of the various tools available to rheumatologists in clinical trials and routine care and their practical differences is important to progress in patient evaluation and management. The tool that is easiest for both the patient and the physician to use and that still provides important treatment response and prognostic information has the best chance to be consistently and successfully applied by busy clinicians.

The treatment of rheumatoid arthritis (RA) has substantially changed over the last decade. These changes have not been limited to the use of newer therapies that have become available over the last 10 years. Our understanding of the long-term implications of active disease and the associated mortality and morbidity with RA has led to a paradigm shift, where early and aggressive treatment has become the goal and cornerstone of effective RA management. Methotrexate (MTX) emerged as a drug of choice in the mid-1980s. During that era, however, the majority of patients were treated with parenteral gold and other only modestly effective drugs, such as penicillamine, sulfasalazine, or hydroxychloroquine. Combination treatment was rare, and it was considered only when patients failed their first disease modifying antirheumatic drug (DMARD) regimen.

Initially, DMARDs were reserved for patients showing evidence of advanced disease, erosions, and failing nonsteroidal anti-inflammatory drugs (NSAIDs). When one DMARD failed, patients were switched to another DMARD, rather than having the new medication added to the current treatment. Aggressive treatment programs evolved parallel to the introduction of MTX. Initial use was hampered by worries related to toxicities that have been shown since to be milder than previously thought. MTX was not the initial DMARD prescribed in most cases, early on; however, until recently, sulfasalazine was the most commonly used DMARD in Europe.

Three important clinical factors have led to a more aggressive approach in the treatment of RA: (1) RA is now recognized to be associated with significant mortality, morbidity, diminished quality of life, and disability; (2) Aggressive treatment has been shown to be more effective in improving both symptoms and quality of life measures; and (3) DMARD treatment has been documented to effectively retard radiographic progression of disease.

One of the more important studies of the last decade, the TICORA (tight control of rheumatoid arthritis), demonstrated that with tight control of disease activity by using standardized disease assessment instruments and applying adjustments to treatment according to preset goals, it was possible to achieve high degrees of remission, even with traditional DMARDs.

Rapid progress in the treatment of RA is exemplified not only by the fact that current drugs are being better utilized and applied but that new medications are available and more are on the way. The main challenge remains in the identification of those patients who are responding to treatment and in objectively quantifying their responses or nonresponses. This
Rheumatology is different from some other subspecialties; composite scores are usually required in rheumatology, reading or cholesterol level, to adequately monitor treatment. However, this awareness stands in contrast to what is practiced in the “real world.” Rheumatologists use few quantitative measures in making clinical decisions. In the United States, fewer than 10% of rheumatologists give patients questionnaires in routine clinical care, and fewer than 15% perform a formal joint count at each visit.

Evidence-based medicine has become the gold standard of modern medical practice; however, practicing clinicians often depend primarily upon their own impressions or the impressions of trusted colleagues of what has worked in the past, sometimes taking into account the outcomes of widely publicized randomized control trials (RCTs). Substantial evidence shows that the majority of the patients seen in routine care would not qualify to participate in contemporary RA clinical trials because of the restrictive inclusion and exclusion criteria. In addition, the trials are usually of short duration, typically less than a year, and do not provide information about important long-term outcomes, such as work disability, joint replacement surgery, and mortality. Hence, it becomes crucial to be able to follow and document the progress of patients under routine care, where a large majority of RA patients are seen and managed, using a tool that has been shown to predict and to monitor response to treatment.

The Health Assessment Questionnaire (HAQ) and its derivatives have been shown to be the best predictors of functional and work disability, cost, joint replacement surgery, and mortality. As questionnaires, they are at least as good as joint counts, radiographs, and laboratory tests in predicting these outcomes. In addition, patient questionnaires can be used in all rheumatic diseases, including osteoarthritis, systemic lupus erythematosus, fibromyalgia, scleroderma, and ankylosing spondylitis.

Rheumatology is different from some other subspecialties in that there is no one measure, such as a blood pressure reading or cholesterol level, to adequately monitor treatment. Composite scores are usually required in rheumatology, in general, but especially in RA, because no one measure that can be used in all patients. Hence, various outcome measures are used in RCTs and are recommended for use in routine clinical care. The American College of Rheumatology (ACR) Core Data Set was developed to provide a consistent group of outcome measures for RA. ACR20, 50, and 70 responses have been used and are good tools, with some differing opinions as to which one is more clinically relevant, however it is cumbersome to use in real world clinical care. This has led to alternatives being developed for both RCTs and clinical care (Table 1). Recently, ACR has also created the hybrid ACR score, in part to develop a tool that still uses the ACR Core Data Set and ACR20, 50, and 70 measures, and to create an instrument that is more sensitive to change. However, the difficulties of the current ACR measures, being hard to use in routine care and being a change score rather than a current activity level score, continue to be problematic with the new hybrid measure.

The Disease Activity Score (DAS) and its derivatives, DAS28 (a 28-joint count) and DAS-CRP (using CRP in place of ESR), are widely used in RCTs. The advantage of providing a score for current disease activity, rather than a change score, as in ACR20, 50, and 70, makes the various DAS scores a more “true” reflection of the patient’s current disease status. However, the DAS requires a calculator to compute, using a complicated formula. In spite of the fact that a web site provides a scoring tool, this and the fact that a minimum 28-joint count by the physician is required for the score, has led to the DAS rarely being used in clinical practice unless mandated. In some European countries the DAS is mandated for regulatory reasons in the approval of biologic agents for treatment.

The Simplified Disease Activity Index (SDAI) and an even further simplified version (no acute phase reactant needed), the Clinical Disease Activity Index (CDAI), have been proposed. Both tools are strongly correlated with DAS, but this is not surprising since they share most of the components of DAS. CDAI has the advantage of calculation at the time of the patient visit, as it does not require a laboratory test, and the calculation required is a straightforward addition rather than a complicated formula.

The Global Arthritis Score (GAS) is a sum of three measures, patient pain, the raw mHAQ score, and tender joint count, and is closely correlated with both the SDAI and DAS. Although GAS is a simple addition of the three

| Table 1 Comparison of Composite Scores Commonly Used in RA |
|-----------------|----------------|----------------|----------------|----------------|----------------|
| DAS28 | SDAI | CDAI | GAS | RAPID | ACR20 |
| Swollen joint | + | + | + | + | + |
| Tender joint | + | + | + | + | + |
| Physician global | + | + | + | + | + |
| ESR/CRP | + | + | + | + | + |
| Patient global | + | + | + | + | + |
| Functional score | + | + | + | + | + |
| Pain | + | + | + | + | + |
different scores as well, it includes a joint count component that is time consuming and is rarely done by rheumatologists, as previously mentioned.

The RAPID instrument (Routine Assessment of Patient Index Data) was developed with the aim of solving an important problem in the monitoring of patients in clinical care: ease of use for both patients and rheumatologists and performance that was equal or better than other available scores. This index of only three patient-reported outcome measures from the Core Data Set, physical function, pain, and patient global estimate of disease activity (Fig. 1), distinguishes active from control treatments in clinical trials as effectively as ACR or DAS criteria.18,19

The calculation of the score does not require “gadgets,” blood test results, or a joint count. It also takes less time to score than a 28-joint count, DAS28, or HAQ scoring20,21 and is highly correlated in the routine care setting with DAS28 and CDAI.19

The need to use a tool to assess RA patients is evident from many perspectives. While all of the measures discussed above perform within the same range of response and are robust, the most user-friendly measures have the best chance of succeeding and improving patient care as well as making efficient use of rheumatologists’ time. We currently use the RAPID in our clinics and some private practices, as well as train our fellows to do the same. RAPID is by far the easiest tool to use, takes the least amount of time, and provides information that is as well-correlated with response as the harder-to-use tools, for example, DAS, DAS28, GAS, CDAI, and SDAI. With more hands-on experience, most rheumatologists, we believe, would find RAPID a useful and acceptable tool to use in the routine clinical care setting.

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Disclosure Statement
Yusuf Yazici, M.D., participates in the speaker bureau for the companies of Pfizer, Amgen, Boehringer Ingelheim, Genentech, and BMS; consults for Roche, Celgene, Schering Plough, and BMS; is an advisory board member to Centocor, BMS, and Genentech; and has received educational grants from Abbott, Centocor, and Genentech.