Guiding Optimal Therapy with the Use of Disease Activity and Functional Instruments: Lessons from the Clinical Laboratory

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ABSTRACT. Proper assessment and aggressive treatment of patients with rheumatoid arthritis (RA) are the key to improved longterm outcomes. The most important diagnostic and monitoring principles for RA include the assessment of inflammation, disease activity, collateral damage from comorbid diseases, and the improvement of patient function and quality of life. A number of different assessment tools are available for physicians to use during routine examination of patients with RA; these instruments will be detailed with suggestions based on proceedings from a satellite symposium at the American College of Rheumatology (ACR) 2006 Annual Meeting. Audience Response System questions and answers for this topic, which may help other clinicians decide which assessment tools to use in their practices, are included. (J Rheumatol 2007; 34 Suppl 79:3-8)

Key Indexing Terms:
TREATMENT RHEUMATOID ARTHRITIS EXAMINATION DIAGNOSIS

INTRODUCTION

Rheumatoid arthritis (RA) is a complex immunologic disease, and proper assessment of a patient's clinical status can be very challenging. Quantitative measures to determine the extent of disease burden have led to major advances in the prognosis and management of RA, and the use of assessment tools not only improves outcomes but may eventually be required by governmental and third-party-payer systems in a "pay for performance" practice environment.

Which assessment instruments are accurate and easily adapted for daily use? How have patient-reported outcome instruments revolutionized the assessment of patients with RA?

TIGHT CONTROL LEADS TO OPTIMAL OUTCOMES

In everyday practice, clinicians aim for attaining a certain outcome in disease management and then optimize patient behavior or titrate medications in order to achieve that outcome. In the treatment of diabetes, one assessment tool is hemoglobin A1C level. This disease management model has been extensively studied and provides some valuable lessons that are applicable to most disease states, particularly chronic, systemic ones like RA and diabetes mellitus. The Diabetes Control and Complications Trial was a large study with over 1400 patients with type 1 diabetes. The goal of this clinical trial was to compare aggressive management of A1C levels with conventional management to keep A1C levels as close to normal as possible[1]. The results of the study demonstrated that the patients who were aggressively managed not only were healthier than the patients who were conventionally managed but also had a much lower risk of comorbid diseases, such as retinopathy, kidney disease, and cardiovascular events[1].

These lessons also can be shown in the treatment of RA. Clinicians should aim for a specific clinical goal (e.g., remission), with the implementation of tight control, to optimize the patient's disease outcome.

MEASURING THE SUCCESS OF RA TREATMENT

In RA, the 4 important global indicators for physicians to monitor are inflammation, disease activity, collateral damage (e.g., atherosclerosis and osteoporosis), and function and quality of life (Figure 1). All clinicians should keep these 4 in mind when treating every patient.

One of the first steps for all clinicians is to strike early. In Europe, early arthritis centers focus on diagnosing patients early in the course of RA. To attain this goal, the early arthritis centers foster strong partnerships with primary care physicians so that patients are diagnosed early and receive early, aggressive treatment. It has been shown that early, aggressive treatment of RA can significantly reduce radiographic progression[2]. Coupled with early diagnosis and treatment, tight control of patients' disease, as discussed below, should be implemented via utilization of various disease assessment tools, with regular monitoring.

It is difficult to predict the outcome of a patient with RA early in the disease course, because there is not one

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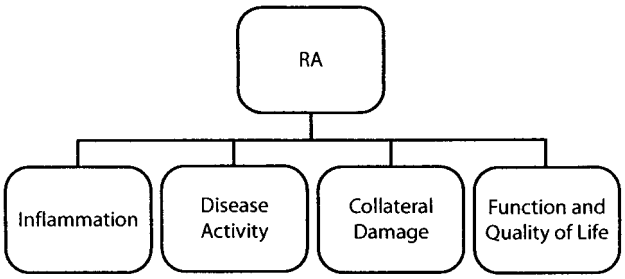

Figure 1. Measures of RA.

definitive early test for RA. Clinicians can monitor rheumatoid factor (RF), antibodies to cyclic citrullinated peptide (anti-CCP), and the shared epitope HLA-DRB1, or conduct imaging studies to look for early erosion[2]. Any of these evaluations may help predict the patient's potential course of RA. In general, some of the clinical and laboratory findings that are correlated with a poor prognosis include the disease severity at presentation, including the level of inflammation, number of joints involved at onset, evidence of early joint damage, and extent of functional limitation such as inability to work. The presence of RF, anti-CCP antibodies, elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), or genetic markers such as HLA-DR1 also correlate with a poor outcome[2].

Another way to assess damage is to perform imaging studies, such as x-ray, ultrasound, and magnetic resonance imaging (MRI). Conventional radiographs are still the most commonly used tool to examine radiographic damage. Radiographs are relatively inexpensive compared with MRI and ultrasound, but both MRI and ultrasound are more sensitive and can determine whether an erosion is present earlier than a radiograph (Table 1)[3,4].

Conventional radiography has an established role in identifying progressive joint damage in RA, although it is insensitive to the presence of synovitis and may not detect early erosions. Radiography should be performed yearly in order to detect the advent of new erosions developing on the present regimen. If the disease is active and current radiographs show no new erosions, and further information is needed to convince the physician and the patient to change medications, an ultrasound or MRI may be helpful. In contrast, both MRI and ultrasound can detect early inflammatory challenges as well as early erosions, in some instances up to 2 years earlier. Limitations of the newer imaging technologies include their cost and the lack of highly qualified personnel. The latter leads to intraobserver and technical variability. These imaging modalities may be utilized to monitor radiographic progression since optimal response to therapy includes an inhibition of radiographic progression. With the use of biologic therapies, a disconnect between radiographic progression and clinical response has emerged whereby an effect on radiographic progression has been noted even in the absence of a clinical response[5-7].

RA is an inherently aggressive disorder associated with serious comorbidities. Patients with RA are more likely to have cardiovascular disease, including myocardial infarction and stroke[8]. They have a 25 times increased risk of lymphoma, mortality rates, and osteoporosis compared to healthy controls[8]. Physicians must be aware of these potential problems, help control the traditional risk factors, and treat patients early and aggressively.

Improvement in physical functioning is an important goal that can be monitored using the Health Assessment Questionnaire (HAQ)[9]. The HAQ is an arthritis-specific, patient-reported outcome assessment tool that is easy to use and available in many languages[9]. The HAQ Disability Index (HAQ-DI) evaluates the patient's ability to perform activities of daily living and correlates with damage, work disability, premature mortality, and costs. The HAQ-DI also measures reversible disease activity and irreversible accrued damage. A sample 8-question HAQ is shown in Figure 2. The simplicity of this

Table 1. Comparisons of imaging techniques.

Imaging Technique	Benefits	Limitations
Conventional radiography	Established role in identifying progressive joint damage	Insensitive to soft tissue lesions (synovitis) Does not detect early erosions
MRI	Detects early inflammatory changes	Expensive Need for highly qualified personnel May require the use of contrast agents
Ultrasound	Visualizes soft tissue inflammatory processes and early erosions Increased sensitivity to minor changes Inexpensive Does not require use of radiation	Intraobserver and technical variability Use of different machines results in limited reproducibility

In the PAST WEEK, how much pain have you had? (circle number or mark through the line below)

NO PAIN 0 1 2 3 4 5 6 (7) 8 9 10 MOST SEVERE PAIN

Mild Moderate Severe

TODAY ARE YOU ABLE TO:	No Difficulty	Some Difficulty	Much Difficulty	Cannot Do
Dress yourself, including laces and buttons?	0	1	(2)	3
Get in and out of bed?	0	1	2	(3)
Lift a full cup or glass to your mouth?	0	1	(2)	3
Walk outdoors on flat ground?	0	(1)	2	3
Wash and dry your entire body?	0	1	(2)	3
Bend down and pick up clothing from the floor?	0	(1)	2	3
Turn regular faucets on and off?	0	(1)	2	3
Get in and out of a car?	0	1	(2)	3

Figure 2. Sample HAQ.

questionnaire gives the physician an excellent idea of how the patient is functioning.

It also is important to normalize the inflammatory "thermostat" as soon as possible. Inflammation can be assessed by examining a number of variables, including tender joint counts (TJC) and swollen joint counts (SJC), acute-phase reactants, and hemoglobin levels, to investigate for anemia and thrombocytosis, which are a reflection of the cytokine burden. Other indices of disease activity that physicians can use include the Disease Activity Score (DAS), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and the Global Arthritis Score (GAS). Any of these indices will work well, so physicians can choose the one with which they feel the most comfortable.

Figure 3 shows the audience response for the following question: Which of the following do you use in your regular care of patients with RA?

Recently, 2880 practicing rheumatologists were sent an invitation to participate in a 33-question online survey from which information on practicing behavior and monitoring of patients was garnered[10]; 40% (1023) of the invited physicians responded. Respondents were asked how frequently they used selected indices and which indices they used. The results revealed that 88% of respondents frequently monitored morning stiffness (88%); 75% utilized a patient-focused joint examination; 70% relied on laboratory tests, such as complete blood count, ESR, and CRP; 51% ordered yearly hand radiographs; 39% assessed patient global/patient pain; and 32% used the physician's global assessment. Only 27% of respondents measured TJC or SJC and 15% employed HAQ assessment. Amazingly, only 6% of respondents used the DAS score to monitor response to therapy and less than 3% measured ACR20 scores. Only 1% of respondents used ultrasound for evaluating erosions[10]. The survey shows

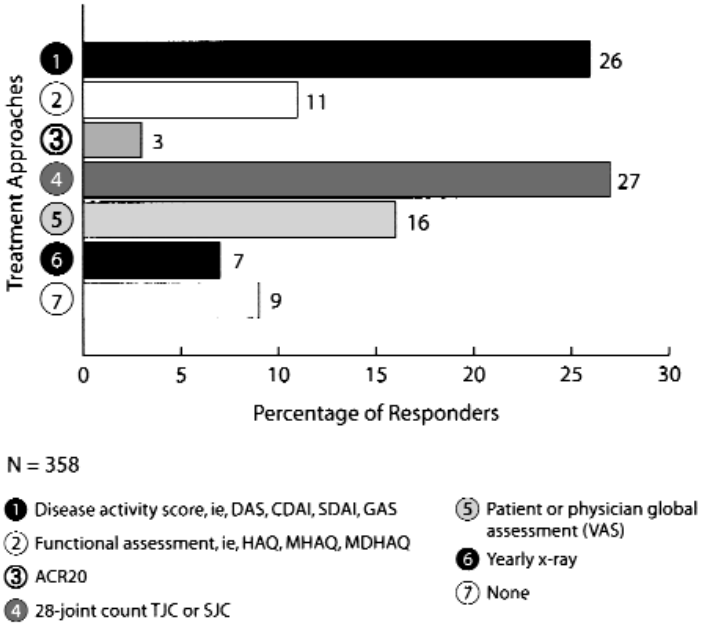

Figure 3. Audience response from the ACR 2006 symposium.

that validated tools and composite indices are not being used to guide clinical decision-making despite 2 landmark trials [the Tight Control for Rheumatoid Arthritis (TICORA) study[11] and the Behandel-Strategieën (BeST) study[12]] that demonstrate a clear benefit and achievement of optimal patient outcomes with their use.

RA disease activity measures

Several validated assessment tools, each with benefits and limitations, are available for use in everyday clinical practice. These are summarized in Table 2.

ACR scores are frequently measured in clinical studies. They are useful for clinical trials, but measure relative change, not disease status at a given point in time; therefore, they are not practical in clinical practice. The DAS, which requires measurement of either ESR or CRP level, measures disease activity at a given point in time. The DAS has limited usefulness in the office setting unless the ESR or CRP levels are measured prior to the office visit and the results are available at the time of the visit. The DAS score requires a complex equation, and a low DAS score (indicating remission) is possible even if the patient has persistent symptoms[13]. The SDAI gives a measure of disease activity at a given point in time and uses a much simpler calculation. Five factors are used to calculate the SDAI: SJC, TJC, patient global assessment, physician global assessment, and CRP level. Its usefulness in office settings is dependent on obtaining a CRP level prior to the office visit[14]. The CDAI and GAS are the most suitable for routine use. The CDAI requires a simple calculation similar to the SDAI, but it does not require measurement of acute-phase reactants. It measures disease activity at a

Table 2. Benefits and limitations of validated assessment tools.

Index	Benefits	Limitations
ACR	Useful for efficacy studies in clinical trials	Measures relative change but not disease status at a given point in time
DAS (includes ESR)	Measures disease activity at a given point in time	Limited usefulness in office setting unless ESR level drawn prior to office visit so ESR level is available for calculation Complex equation used in calculation of score Low DAS score possible with persistent symptoms
SDAI (includes CRP)	Measures disease activity at a given point in time Simple calculation	Limited usefulness in office setting unless CRP level drawn prior to office visit so CRP level is available for calculation
CDAI	Measures disease activity at a given point in time but without CRP or ESR, negating need for previsit blood testing Simple calculation	Does not measure acute-phase reactants
GAS	Measures disease activity at a given point in time but without CRP or ESR, negating need for previsit blood testing Simple calculation	Does not measure acute-phase reactants Limited clinician experience with new tool

Table 3. Outcome measures in RA

	ACR20	DAS28	SDAI	CDAI	GAS
Patient function	3				3
Patient pain	3				3
Patient global	3	3	3	3	
MD global	3		3	3	
TJC	3	3	3	3	3
SJC	3	3	3	3	
ESR or CRP	3	3	3		

TJC: tender joint count, SJC: swollen joint count.

Table 4. Revised definition of outcomes in RA.

	DAS28	SDAI	CDAI	GAS
Remission	≤ 2.4	≤ 3.3	≤ 2.8	≤ 3
Near remission (low disease activity)	≤ 3.6	≤ 11	≤ 10	≤ 7
High disease activity	> 5.5	> 26	> 22	> 20

given point in time[14]. The GAS also measures disease activity at a given point in time and does not use the CRP or the ESR. It uses a simple calculation that takes into account the patient's pain, a modified HAQ result, and TJC. Table 3 shows a comparison of these different outcome measures.

It should be noted that each of these outcome measures correlates well with the others and has slightly different definitions of remission, near remission (low disease activity), and high disease activity. If you plan to switch from one tool to another, this must be taken into account when evaluating the patient's score (Table 4)[12].

Use of RA disease activity measures in practice: proofs of principle

Two clinical studies utilized validated clinical disease activity measures and demonstrated their usefulness for everyday clinical practice: the TICORA study[11] and the BeST study[12].

The TICORA study examined intensive versus routine control of disease activity in RA[11]. The objective of the study was to determine whether intensive control of RA with nonbiologic disease modifying antirheumatic drugs (DMARD) would result in significantly better outcomes than routine care. This clinical trial studied 110 patients with RA duration less than 5 years but with active disease and a high DAS score (> 2.4); the patients were treated for 18 months. In the intensive-treatment group, the physicians carried out a monthly DAS assessment with a structured escalation of therapy. In the routine-care group, patients were managed at the discretion of the treating physician, who saw the patient every 3 months, but did not formally measure disease activity. The results showed that aggressive treatment resulted in significantly better clinical and functional outcomes after 18 months compared with the routine-control group. Seventy-one percent of patients in the aggressive-care group achieved an ACR70 response compared with 18% of patients in the routine-care group ($p < 0.0001$). The DAS and HAQ scores also were better, and the total increase in Sharp score was less (4.5 for aggressive care vs 8.5 for routine care; $p = 0.02$) for the aggressive treatment group[11].

In the BeST study, the objective was to evaluate the clinical and radiologic outcomes after 2 years of 4 different treatment strategies for early RA[12]. In this study, 508 patients were randomized to one of 4 different treatment strategies: sequential monotherapy with DMARD, step-up combination therapy with DMARD, initial combination therapy with DMARD and prednisone, or initial combination therapy with DMARD and the tumor necrosis factor inhibitor infliximab. Treatment adjustments were made every 3 months in an effort to obtain a low DAS44 (≤ 2.4). The results at the 2-year followup revealed that clinical remission was similar in all 4 groups but that the more aggressive combination treatment (with prednisone or infliximab) was associated with better radiographic outcomes (change of mean Sharp-van der Heijde score = 1.0 for either of the aggressive combination treatments vs 2.0 for the sequential or step-up therapies; $p = 0.004$). Relative to sequential or step-up therapy, combination therapy (with either prednisone or infliximab) was associated with more rapid clinical and functional improvement, lower relative risk for disease progression, and fewer treatment adjustments[12].

Conclusions

Assessment and management of a patient with RA is a complex process that requires ongoing evaluation of multiple disease characteristics. Regular assessment using appropriate validated instruments enhances a clinician's ability to achieve tight control and optimal patient outcomes. In some jurisdictions, third-party-payer systems have begun documentation of validated assessment tool use as part of their "pay for performance" strategy, so it is no longer a question of whether to use such instruments but rather which of the assessment instruments are

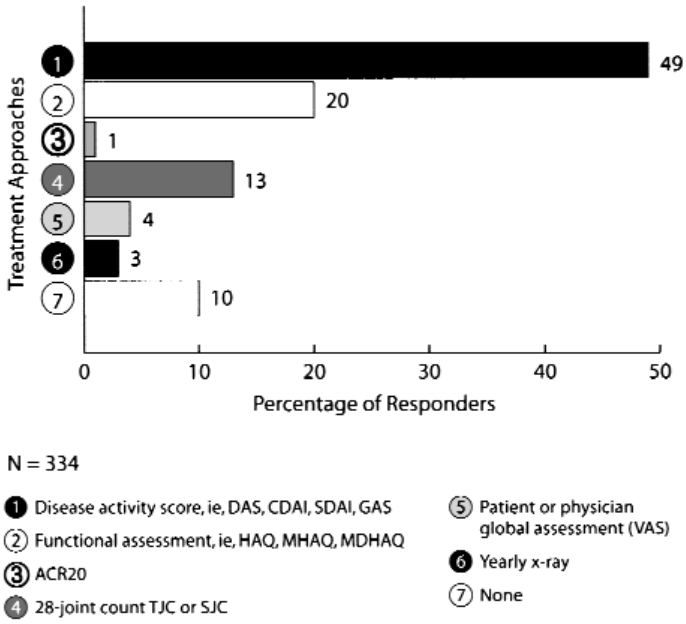

Figure 4. Audience response from the ACR 2006 symposium.

the most accurate or easily adapted to clinical and patient use.

Figure 4 shows the response of the audience at the satellite symposium at the ACR 2006 Annual Meeting to the following question: Which of the following will you use in the future in your regular care of patients with RA?

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