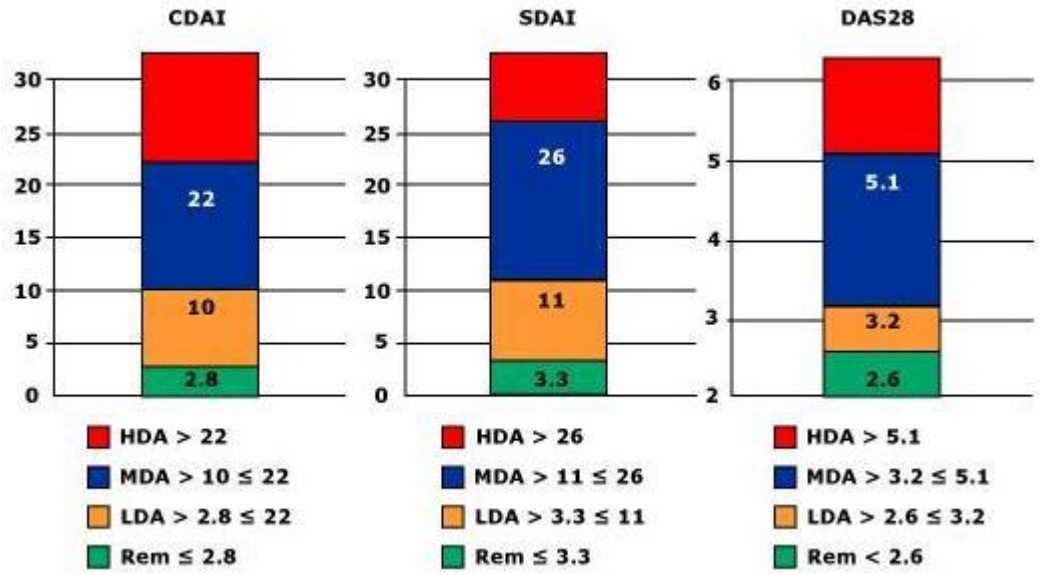
SDAI and other Rheumatoid Arthritis Activity Scores.

Disease activity categories and respective cut-points for the CDAI, SDAI and DAS28



Ranges: CDAI = 0 to 80; SDAI = 0 to 100; DAS28 = 0.5 to 9. HDA: High Dose Activity; MDA:
Moderate Dose Activity; LDA: Low Dose Activity; CDAI: Clinical Disease Activity Index; SDAI:
Simplified Disease Activity Index; Rem: Remission; DAS 28: 28 Joint Disease Activity Score.

Assessment of rheumatoid arthritis activity in clinical trials and clinical practice

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INTRODUCTION — Approaches to the management of rheumatoid arthritis (RA) have evolved as an increasing number of effective disease-modifying anti-rheumatic drugs (DMARDs) have become available. The goals of DMARD use are not only to ameliorate the symptoms and signs of active RA, but also to prevent structural joint damage and avoid functional impairment. The development of new antirheumatic therapies—including biologic agents targeted against specific components of the immune system—has required the availability of instruments that permit the assessment of disease activity and the response to therapy. Regardless of whether patients are evaluated in the context of a clinical trial or longitudinal clinical practice, the successful application of DMARD therapy requires that the goals of therapy be specified in advance and that the specific choice of DMARDs be revisited on a regular basis.

Clinical indicators employed in the assessment of RA activity are discussed here. The roles of both individual variables (eg, swollen joint counts and acute phase reactant measurements) and composite indices for disease activity assessment are considered, as are definitions of remission and criteria for clinically significant responses. Although much of the discussion centers around clinical trial outcome measures, we also provide recommendations for clinical practice.

A number of other topic reviews are related to the discussion of RA disease activity and complement the information provided here. As examples:

- The clinical features of RA, including the concept of disease remission and the importance of distinguishing disease activity from structural joint damage are discussed elsewhere. (See "Clinical features of rheumatoid arthritis").

- Functional capacity and functional disability indices, which relate to a large extent to the degree of RA disease activity, are reviewed separately. (See "Disease outcome and functional capacity in rheumatoid arthritis").

- Descriptions of a variety of biologic markers of disease activity, including those with established clinical utility and those that are of investigational interest are presented elsewhere. (See "Clinically useful biologic markers in the diagnosis and assessment of outcome in rheumatoid arthritis" and see "Investigational biologic markers in the diagnosis and assessment of rheumatoid arthritis").

- The management of RA, including pharmacologic and nonpharmacologic as well as surgical interventions is surveyed separately. (See "Overview of the management of rheumatoid arthritis").

GENERAL PRINCIPLES — The conceptual framework for the assessment of disease activity in RA is defined by several principles.

- Active RA leads to severe joint destruction, functional disability, and impaired health status [1-8] , particularly if sustained at high levels for prolonged periods of time. Thus, reduction of clinical disease activity through prudent DMARD use is an essential therapeutic aim.

- Monitoring disease activity at regular, short-term intervals (not to exceed three months) and appropriate modifications of DMARD therapy improve radiographic and functional outcomes in patients with RA [9-11] .

- Functional impairment may relate to both active RA, manifested by symptoms such as pain, swelling, and stiffness of the joints, and to structural joint damage occurring as the consequence of previously active disease [3,5,12,13] .

- Therapeutic goals are the achievement of remission (ie, the virtual absence of disease activity) or the lowest possible state of disease activity. In the majority of RA patients, the achievement of disease remission corresponds to the cessation of joint damage [14,15] .

- With few exceptions [16] , clinically active RA and the processes leading to joint destruction are linked, such that damage usually progresses in the presence of active disease [17-23] .

The following sections describe individual elements that are assessed in order to determine RA activity, the concepts of composite indices and response criteria, and the definitions of low disease activity and remission.

INDIVIDUAL VARIABLES OF DISEASE ACTIVITY — Common indicators of disease activity in RA include the following measurements:

- Swollen and tender joint counts
- Pain
- Patient and evaluator global assessments of disease activity
- Erythrocyte sedimentation rate and C-reactive protein (ESR, CRP)
- Duration of morning stiffness
- Fatigue
- Measures of function (eg, the Health Assessment Questionnaire)
- Health status (eg, the Short Form 36)

Core sets of disease activity variables — Beginning in the 1990s, several groups defined core sets of disease activity variables. The American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and a group of investigators representing both the World Health Organization (WHO) and International League of Associations of Rheumatology (ILAR) all published similar but slightly different core sets of activity variables [24-26] . The methods used to identify these variables were driven by clinical data and met several criteria for validity[27-29].

All three core sets include swollen and tender joint counts, patient assessment of pain, patient global assessment of disease activity, and a measure of the acute phase response. As an example, the ACR core data set includes a total of seven measures: three performed by the evaluator (swollen joint count, tender joint count, and global assessment of disease activity); three collected by patient self-report (functional status, pain, and global health status); and a laboratory measure (either an ESR or CRP). The ACR and WHO/ILAR core sets both include evaluator global assessments of disease activity and physical function. In contrast, in the EULAR core set, physical function is regarded as an outcome variable rather than a process variable.

Swollen and tender joint counts — Joints are typically assessed according to two characteristics: 1) soft tissue swelling and effusion (the swollen joint count); and, 2) pain on pressure or motion (the tender joint count). In general, neither the weighting of joints by their size (ie, the cartilage surface area) nor grading them by degree of swelling or tenderness confers validity and reliability [30,31] .

The 28 joint count has become a standard for use in both clinical practice and clinical trials [31-34] . The 28 joint count excludes assessments of the foot and ankle joints, because the interpretation of swelling and tenderness in these joints is confounded frequently by disorders other than RA [31,33,34] . Although the 28 joint count has been criticized for leaving out assessment of the feet, it has been thoroughly validated and employed reliably in clinical trials and other analyses [35,36] .

Pain — Pain is usually measured by visual analogue scales [34-36] , which most often use horizontal 100 mm lines. Patients indicate their degree of pain (typically over the preceding week) by placing a mark between "no pain" (left end, 0 mm) and excruciating pain (right end, 100 mm). Alternatives to visual analog scales include numerical rating scales (ranging from 0-10) and categorical scales (eg, 5-point Likert scales), both of which are reliable and sensitive to change [37-39] .

Patient and evaluator global assessments — Global disease activity rated by either the patient, the evaluator, or both (and termed, respectively, the PGA or EGA, as

appropriate) is assessed in a similar manner using visual analog scales, numerical rating scales, or Likert scales. Measuring the PGA acknowledges the importance of patient-reported outcomes. Whereas the EGA typically integrates information from both subjective and objective variables, the PGA is considered a subjective measure. Because patients are more likely than are medically-trained evaluators to construe functional disability as a manifestation of active disease and because medically-trained evaluators have greater context for comparison with other RA patients, PGAs are usually scored at higher levels than are EGAs.

Acute phase reactants — Acute phase reactant levels, particularly the ESR and CRP, constitute the most objective disease activity measures. Acute phase reactant levels correlate well with both clinical disease activity measurements and radiographic progression of joint damage [2,6,40-42] . The ESR and CRP are the two biomarkers used most widely to assess disease activity. These tests are widely available, relatively inexpensive, reflective of the cascade of inflammatory events associated with active RA, and the CRP in particular is well standardized. Measurements of individual components of this response, e.g., levels of the interleukin (IL)-1 beta, IL-6, or TNF-alpha, are not more useful in assessing RA activity and are prone to greater variation from laboratory to laboratory.

Other variables — Other variables associated with disease activity include the duration of morning stiffness, degree of fatigue, and the reduction in functional capacity. Morning stiffness is not contained among the core set variables because of its higher variability and lower sensitivity to change compared to other measures. A variety of patient-reported instruments are available to measure levels of fatigue, including the vitality/fatigue scales that constitute part of the SF-36. More commonly, however, fatigue is assessed simply through the use of a visual analog scale.

COMPOSITE INDICES FOR DISEASE ACTIVITY ASSESSMENT — The individual variables outlined above reflect major characteristics of the disease within the population of RA patients as a whole. Given the heterogeneity of RA, however, the predominance of these indicators may be highly variable across individual patients, and may even vary with time within individual patients. As a result, the evaluation of a single core variable (eg, the ESR) in patients with RA would not reflect accurately the full spectrum of the disease. In addition, the evaluation of all variables within core sets often leads to heterogeneous responses and substantial methodological problems [27-29,43] . Thus, "composite" indices combining several core set variables have been developed. Several composite indices are in common use (show table 1). Formulas for calculating the indices vary in complexity, some are challenging to compute [6,32,44-47] . The Disease Activity Score (DAS), its derivative (the DAS28), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) are described in greater detail below.

Disease Activity Score (DAS) — The basis of the DAS was the clinician's decision to raise or lower DMARD doses based on a largely qualitative assessment of disease activity and reflected clinical practice in about 1990 [44] . Several features make the DAS challenging to use in clinical trial and practice settings. First, the DAS employs the Ritchie Articular Index [45] , a measure with major shortcomings in terms of feasibility and reliability, to evaluate joint tenderness. Second, the DAS employs an extensive 44 joint count to record the number of swollen joints. Finally, once the data required to complete the DAS are accumulated, the formula for calculating the score is quite complex, using different weights for each of the variables as well as square roots or logarithmic transformations in the case of some (show table 1). In summary, the original DAS is complicated, not user friendly, and not ideally suited to wide use.

DAS28 score — A modification of the DAS is considerably more practical. The DAS28 eliminated the grading of joints and reduced the number of joints evaluated to 28

[32,47] . Although calculation of the DAS28 still requires a nontrivial calculation, a program available on the Internet facilitates the computation: (www.das-score.nl/index.html).

Ranges of DAS28 scores that correspond to high, moderate, low disease activity, and remission have been proposed (show table 1 and show figure 1). It should be noted that nearly 15 percent of patients with DAS28 scores of 2.6 - the cutpoint for remission - continue to have at least 2 swollen joints; some may have more than 10 swollen joints yet still be categorized as in "remission" using this composite index [7,48,49] . Other composite measures also permit a number of inflamed joints among patients who fulfill criteria for remission.

The major advantages of the SDAI and the CDAI, discussed below, relate to their relative ease of computation.

Simplified Disease Activity Index (SDAI) — The SDAI, which employs five of the core set variables (show table 1) is computed using a linear sum of unweighted, untransformed variables [47] . The SDAI has been validated for use in both clinical trials and clinical practice [7,50,51] . Moreover, it has been shown to have the highest sensitivity and specificity for predicting physicians' decisions to change DMARD therapy in 2005 when compared to other composite scores [51] .

Cutpoints for the various activity states have been established (show table 1 and show figure 1). A cutpoint of 15 for the SDAI had the best combination of sensitivity and specificity (90 percent and 86 percent, respectively) when compared to the treating physicians' decisions to change DMARDs because of active disease in a more recent observational study [51] . The cutpoint for remission, an SDAI of 3.3, does not allow the presence of more than two joints that are swollen or tender.

Clinical Disease Activity Index (CDAI) — A further simplification of the SDAI, the CDAI, does not require the measurement of an acute phase reactant (show table 1 and show figure 1). The CDAI correlates well with other disease activity scores and response criteria, as well as with progression of joint damage and functional impairment [6,47,52] . The advantage of the CDAI is that it facilitates immediate treatment decisions based entirely on clinical criteria. This attribute is useful in clinical trials, since it circumvents the potential problem of lab to lab variation in the measurement of acute phase reactants.

PHYSICAL FUNCTION ASSESSMENTS AS MEASURES OF DISEASE ACTIVITY — Because active RA exerts a substantial effect on physical function, instruments designed to measure physical function are also useful indicators of disease activity. Such instruments, developed for generic use, are employed commonly in clinical trials, less often in clinical practice. The two physical function assessment tools used most frequently are the Health Assessment Questionnaire (HAQ) and the Medical Outcomes Study Short Form-36 (SF-36) [53-56] .

Health Assessment Questionnaire (HAQ) — The complete HAQ is a comprehensive instrument designed to assess patient disability, discomfort, medication side effects, costs, and mortality. Of these components, only the HAQ Disability Index (HAQ-DI) is used frequently in clinical trials and clinical practice. The HAQ-DI, an important component of the ACR core data set for the evaluation of rheumatoid arthritis disease activity and outcome, evaluates patients' ability to perform activities of daily living through their answers to 20 questions designed to assess upper or lower extremity use. These questions are organized into 8 categories: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Each question is answered on a four level scale

of impairment ranging from 0 to 3: 0 = no difficulty; 1 = some difficulty; 2 = much difficulty; and 3 = inability to do.

The final HAQ index, which ranges from 0 to 3, is the mean of scores from all eight categories. HAQ scores < 0.3 are considered normal, however, the mean HAQ of the population rises with age [57] . Higher HAQ scores indicate increasing disability. Although the primary influence on the HAQ is disease activity [5,54] , the score reflects both joint damage and disease activity. The irreversible, damage-related component of disability as assessed by HAQ increases with the degree of joint damage and with disease duration [13] . The smallest clinically important difference in serial HAQ scores has been suggested to be 0.22. Several modifications of the HAQ have been employed in clinical trials and practice [55] .

The Short Form-36 — The SF-36 is a generic, patient-reported instrument designed to assess overall health status [56] . The SF-36, usually utilized to measure patients' quality of life, has been validated in numerous diseases, including RA. The instrument consists of 36 questions organized into 8 domains: physical function, physical role, general health, bodily pain, mental health, social function, vitality/fatigue, and emotional role. Data from these eight domains can be summarized into two categories, a physical component score and a mental component score. SF-36 results are particularly useful for comparing quality of life across cohorts of patients with different diseases, but also correlate well with other measures of RA activity. Increasing SF-36 scores are indicative of improving health status.

PATIENT-REPORTED INSTRUMENTS — Two self-reported instruments are available for the assessment of RA activity. These are known, respectively, as the Rheumatoid Arthritis Disease Activity Index (RADAI) and the Rapid Assessment of Disease Activity in Rheumatology (RADAR) instruments [58,59] .

The RADAI encompasses 5 items, including patient-assessed joint counts. A major detraction of the RADAI, similar to that of the DAS, is its the need for a calculator. In contrast, the RADAR is a brief, two page questionnaire that includes 6 items related to arthritis symptoms, physical function, work impact, psychological status, social health, and satisfaction with health status. Although the use of patient-reported indices of disease activity such as the RADAI or RADAR is appealing in RA, a condition associated with large personal dimensions, these instruments are rarely used in clinical trials and almost never in clinical practice. The patient-reported instruments used most often in clinical trials are global assessments of disease activity (eg, visual analog scales), HAQ scores, and the SF-36.

RESPONSE CRITERIA — Response criteria, defined for both moderate and major changes in disease activity, have been developed for all of the major RA activity assessment indices. Such criteria can be applied to large numbers of patients in the context of clinical trials, and also in gauging the treatment responses of individual patients over time. Response criteria may involve either the comparison of a patient's activity score to a baseline value for that same patient, or the achievement of a certain disease activity state (eg, either remission or low disease activity).

ACR response criteria — An early attempt to define minimal response requirements was provided by the Paulus criteria [60] . These criteria formed the basis for the ACR response criteria [61] , which (in their initial iteration) outlined the parameters of a 20 percent improvement. The ACR20 response, a standard measure for many clinical trials performed since 1995, is defined as improvement of at least 20 percent in the number of both swollen and tender joints, as well as at least 20 percent improvement in three or more of the five remaining core set variables (show table 2)

ACR20 response — The ACR20 response discriminates accurately between the effects of active medications and those of placebo. However, because of improvements in RA treatment, the ACR20 is no longer considered an optimal measure of clinically meaningful change: patients who achieve only ACR20 responses may still have substantial disease burdens from active RA. Moreover, the ACR20 has other potential weaknesses in some applications: 1) it does not measure directly any responses >20 percent in magnitude over baseline; 2) it characterizes the percentage of patients who meet this cutoff, rather than the response of the average patient; 3) it measures the change in patients' disease activity compared with baseline, but does not quantify disease activity at the end of the period of interest.

ACR50 and ACR70 responses — More ambitious criteria for improvements in disease activity have been proposed; namely, the ACR50 and ACR70 responses [62] , corresponding to 50 and 70 percent improvements, respectively. In contrast to ACR20 responses, patients notice dramatic differences following the achievement of ACR50 and ACR70 responses. In clinical trials of biologic agents, DMARDs, or various combinations, the percentage of patients achieving ACR20, 50, and 70 responses with the study agent (or combination of agents) have been on the order of 40 to 80 percent, 25 to 60 percent, and 10 to 40 percent, respectively.

However, as categorical variables, the ACR50 and ACR70 suffer from some of the same drawbacks as the ACR20. Thus, some investigators have attempted to express changes in the ACR core set variables as a continuous measure. One such effort, the ACR-N (N for numeric), judges changes in the following three variables: swollen joint count, tender joint count, and the median of the 5 remaining core set variables, using the 0-100 percent improvement that is the smallest among these three measures [47] . Thus, the ACR-N quantifies the patient response in terms of a single number, providing a continuous variable rather than a categorical one.

In summary, the categorical response criteria embodied in the ACR20, ACR50, and ACR70 measure the frequency of benefit (ie, the proportion of patients receiving a certain treatment that achieve a defined response). In contrast, measuring the mean or median ACR-N improvement facilitates an estimation of the cumulative magnitude of benefit that may be anticipated for a typical patient relative to the baseline disease activity. Both types of measures are useful for certain situations, and in many cases the information they provide are complementary.

EULAR response criteria — The EULAR response criteria are based on the DAS28. These criteria categorize improvement into either good or moderate responses (show table 1) [63,64] .

EULAR good response — For a good response, the decline in score must exceed 1.2 and result in the achievement of low disease activity (ie, DAS28 < 3.2).

EULAR moderate response — A moderate response, on the other hand, may be achieved in three ways:

- A decline in the DAS28 by at least 1.2; or
- A decline of > 0.6 plus a shift from high disease activity (ie, DAS28 > 5.2) to moderate disease activity (ie, DAS28 < 5.1); or
- A decline of > 0.6 plus a shift from moderate disease activity (DAS28 > 3.2) to low disease activity (DAS28 < 2.6).

Comparisons of the ACR and EULAR Response Criteria indicate that moderate EULAR responses are achieved more often than ACR20 responses in most studies. Good EULAR responses are observed more frequently than are ACR50 responses. There is currently no comparable EULAR equivalent to the ACR70 or the ACR-N (see "ACR response criteria" above).

SDAI and CDAI response criteria — Response criteria have also been derived and validated for the SDAI and CDAI (see "Simplified Disease Activity Index (SDAI)" above, and see "Clinical Disease Activity Index (CDAI)" above) (show table 1) [65] .

Moderate SDAI response — A moderate SDAI is defined as an improvement of 7 points.

Major SDAI response — A major SDAI response is defined as an improvement of 17 points.

Moderate CDAI response — A moderate CDAI response is defined as an improvement of 6.

Major CDAI response — A major CDAI response is defined as an improvement of 14 points.

REMISSION — In concept, the state of remission constitutes a clinical condition in which no active disease is present. As noted, current definitions of disease remission technically permit within their parameters some degree active disease (show table 1) [7,51,66,67] . The identification of remission is hampered practically by the presence of irreversible joint damage, which may lead to abnormalities confused with residual disease activity. In a similar manner, comorbidities such as fibromyalgia or osteoarthritis may confound the designation of remission. Because progressive joint destruction may occur and function may decline, albeit at comparatively slow rates, when disease activity persists even at a low level, stringent criteria are important as a means of distinguishing remission from low disease activity [4,7,10,68] .

SUMMARY AND RECOMMENDATIONS FOR CLINICAL PRACTICE

- The three major points supporting the use of disease activity measures in clinical practice to try to achieve a goal of remission are the following: 1) Active RA leads to severe joint destruction, functional disability, and impaired health status; 2) Monitoring disease activity at regular, short-term intervals and appropriate modifications of DMARD therapy leads to significant functional and radiologic improvements; and, 3) Joint destruction frequently progresses even in states of low disease activity.

- Several indicators of disease activity are typically assessed in clinical trials of therapeutic agents in patients with RA. Among them, the most often measured are: swollen and tender joint counts, pain, patient and evaluator global assessments, acute phase reactants (ESR, CRP), duration of morning stiffness, fatigue, measures of function (eg, the HAQ), and of health status (eg, the Short Form 36). (See "Individual variables of disease activity" above).

- Various sets of individual measures have been characterized that are useful for assessing the efficacy of drug treatment of RA. These core sets include those developed by the ACR, EULAR, and WHO/ILAR . (See "Core sets of disease activity variables" above).

- The Disease Activity Score (DAS) and related composite indices of disease activity (eg, DAS28, SDAI, and CDAI) represent indices that provide a timely aid to clinical decision making. The SDAI and CDAI are easier to calculate than the DAS or DAS28. (See "Composite indices for disease activity assessment" above).

- Responses of groups of patients to treatment in clinical trials may be based on a categorical criterion (eg, an ACR50 response, a EULAR good response, or a CDAI/SDAI major response) or the mean of a numeric index of disease activity (eg, ACR-N, DAS, SDAI, or CDAI). DAS, SDAI, and CDAI provide measures of disease activity while the ACR-N represents improvement from baseline. (See "Response criteria" above).

- With some preparation and minor modifications of the usual work flow in clinical settings, all of the variables comprising core data sets for RA activity assessment can be collected in a standard fashion: 1) Tender and swollen joint counts can be obtained by any health professional with appropriate training; 2) Visual analogue scales for patient and evaluator global assessments of disease activity require less than one minute to complete (show figure 2); 3) Routine laboratory testing of the ESR, CRP, or both is inexpensive and widely available; 4) HAQ-DI assessments may be completed by patients in the waiting room.

- We suggest use of the CDAI to help guide treatment decisions by clinicians caring for patients with RA. The CDAI, a simple numerical sum of swollen and tender joints (using the 28 joint count), the patient global assessment and the evaluator global assessments, has intuitive appeal (see "Clinical Disease Activity Index (CDAI)" above).

- The CDAI can be used for clinical decision making purposes even in the absence of information about acute phase reactants. The ESR or CRP, if available, may be useful in validating the clinician's impressions based on the CDAI or other composite index of choice.

Specific recommendations regarding the therapy of RA are discussed elsewhere (See "Overview of the management of rheumatoid arthritis" and see "Treatment of persistently active rheumatoid arthritis in adults"). The following points with regard to the adjustment of therapies in the context of serial assessments of disease activity should be considered:

- Optimal management of patients with RA and some degree of active disease requires serial assessments. We suggest intervals not greater than every three months.

- Changes in therapy should be entertained as long as patients have not reached low disease activity ranges, defined according to the clinician's composite activity index of choice (show table 1). As an example, if a patient has a CDAI score > 10 after three months of a maximal dose of methotrexate and low-dose prednisone, the switch to or addition of another DMARD (eg, sulfasalazine,leflunomide, or the addition of a biologic agent should be considered.

- Choices of additional agents vary according to practice style, insurance considerations, and concerns about the possible adverse events of specific medications, but alterations in therapy designed to produce low disease activity states through longitudinal evaluations are the crux of good clinical care in RA.

- Once a low disease state has been achieved, the clinician and patient should aim for the goal of clinical remission (defined, for example, by a CDAI < 2.8),

balancing the patient's overall health status and goals with the risk of additional therapies.

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