

Evaluation and Documentation of Rheumatoid Arthritis Disease Status in the Clinic: Which Variables Best Predict Change in Therapy

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ABSTRACT. To determine in clinical practice which rheumatoid arthritis (RA) clinical status variables are most associated with a change in disease modifying antirheumatic drug (DMARD) therapy, we studied 26,240 observations from 1905 RA patients occurring over 25 years. Variables included tender joint count, erythrocyte sedimentation rate (ESR), grip strength, visual analog scale for pain, global severity, fatigue and sleep, Health Assessment Question functional disability scale (HAQ), anxiety, depression and morning stiffness. Only the tender joint count required a physician. Observations at which a change in DMARD therapy occurred were compared to those where a change did not occur using generalized estimating equations (GEE) and classification and regression tree analysis (CART). Tender joint count, pain, global severity, and ESR were the 4 variables most strongly predictive of DMARD change. CART modeling indicated a special role for fatigue and sleep disturbance in some patients. These data add support in clinical practice for the ACR core set and the DAS set of variables. In addition, they validate the use of these variables in a practice setting. We suggest a minimum set of evaluations comprising: joint count, ESR or CRP, measures of pain and/or severity, a fatigue scale (fatigue being a surrogate for sleep disturbance), and a measure of function such as the HAQ or modified HAQ. Because only joint count requires physician participation, these evaluations are practical for the clinic, and allow quantitative measurement of RA status. With the use of quantile charts, the comparative status of RA and the change in RA status can be determined easily. (J Rheumatol 2001;28:1712-7)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
DISEASE ACTIVITY

ASSESSMENT

TREATMENT
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There is a considerable discrepancy between clinical trials and clinical practice in the area of disease status evaluation. Highly protocolized, detailed, time consuming, many paged evaluations are the standard of practice in the randomized clinical trial (RCT). In the clinic, there is little time for such evaluations, and clinicians opt for other methods. Fewer than 10% of clinicians use pain scales, fewer use functional status questionnaires, and although joint evaluations seem to be performed to some extent, few formal joint evaluations are recorded in medical records^{1,2}.

If we choose to believe that rheumatologists provide excellent care for patients with rheumatoid arthritis (RA), and there are many reasons to believe this to be true³⁻⁶, how

can this care be provided without the joint measures and questionnaires that have become state of the art over the last decades?

It is worthwhile to look at some of the differences between randomized controlled trials (RCT) and clinical practice. RCT are fundamentally easy: difficult psychosocial issues that play such a prominent role in the clinic are “randomized” away, and the question to be asked is “On average, did the treatment work?” The clinician’s job is much more difficult: at issue is whether a given treatment *will* work or *is working*, in *this* patient, with *all* of the psychosocial and socioeconomic “baggage” that is always present.

Could it be that the RCT research model is uninformed or, in statistical terminology, is underspecified or has omitted variables? Could it be that, in fact, the clinician knows more than the research model? In Bayesian research terminology, the clinician has a reasonable estimate of “priors.” That is, he knows lots of things about the patient that will influence the patient’s outcome but are unknown to the (probabilistic) RCT model. As rheumatologists, we often know which patients are non-compliers, somatizers, non-responders, and responders; we know which patients have other major problems in their lives, which cannot afford our medications, or which are even tenuous about receiving any

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treatment at all. That is, we know more than we can measure or can even say. Finally, the clinician has a special role: not merely to reduce the number of swollen joints, but to pilot the patient as safely, as happily, as successfully as possible through the long journey of rheumatoid arthritis.

This is all well and good. But not all doctors or even rheumatologists are equally able. Increasingly, governmental forces and third party payers are demanding some documentation of what is going on in the rheumatology encounter. The current report investigates which assessments might be appropriate for use in patient care and in documentation of status and change of status in RA. Before we proceed we need to point out that no study has ever examined whether detailed evaluations by questionnaire and physical examination improve outcome or current status of the RA patient being treated by a rheumatologist.

How should patients with RA be evaluated? Two general methods for the evaluation of patients with RA are in general use in clinical trials. The American College of Rheumatology (ACR) improvement criteria evaluate (1) swollen joint count, (2) tender joint count, (3) acute phase reactant [erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)], (4) visual analog scale for pain (VAS), (5) VAS Global Severity, and (6) functional disability [usually a Health Assessment Questionnaire (HAQ) score]⁷. When a patient improved by 20%, 50%, or 70% on at least 4 of 6 of the scales, that patient meets the ACR 20%, 50%, or 70% ACR improvement criteria⁸. An essential feature of the ACR criteria is that it measures change.

A second method for patient evaluation was proposed by van der Heijde and colleagues⁹⁻¹¹. They evaluated patients with recent onset RA and studied which variables best identified patients who began disease modifying antirheumatic drugs (DMARD) compared to those not switching therapy. Swollen joint count, tender joint count, ESR, and patient global severity were identified as the best predictors and a score, called the Disease Activity Index or DAS, was developed based on this careful clinical experience. The HAQ was not used during the van der Heijde studies so it was not tested for inclusion in the DAS.

In contrast to the ACR criteria that were based on change in status, the DAS is based on absolute status. Although other indices have been proposed, these two methods have come to dominate recent clinical trials. The DAS has the added advantage that it can be used in the clinic to evaluate disease activity in the absence of a clinical trial.

These indices, however, do not appear to have caught on in the clinic, and there is no evidence that they are being used as clinical tools except in a very few settings. The *realpolitik* of such scales is defined by clinical practice. We have recently shown that US rheumatologists rarely use HAQ, pain, or global severity indices¹. In addition, very few record formal joint tenderness and/or swelling counts; and for many rheumatologists the ESR or CRP is available only

after the patient has left the clinic¹. There are several other objections to the ACR and DAS methodology. The ACR index measures change as a measure of success, but severe disease status may be more important than change. The DAS index requires complex mathematical calculations or the use of a specialized conversion ruler.

METHODS

Beginning in 1974 and continuing through 1999, all patients (N = 1905) who were seen in the Wichita Arthritis Center completed detailed questionnaires and rheumatic disease examinations. In addition, laboratory and radiographic studies were performed frequently. The total number of observations was 26,240 for an average of 13.8 observations per patient. The Arthritis Center is a private practice outpatient rheumatology clinic. Details of these patients have been reported¹²⁻¹⁵.

Clinical variables. Table 1 displays the variables available to this study. Only 17,211 pain scores were available in VAS format. An older categorical pain scale was used in observations prior to the introduction of the VAS scale. We do not report on that older scale here. Fatigue and sleep disturbance scales were added in the 1990s, hence their reduced number. The HAQ and anxiety and depression scales were introduced in the early 1980s. Only joint count, ESR, morning stiffness, and global severity scales were used from the onset of the data bank in 1974.

Taken as a whole, questionnaire measures form the Clinical Health Assessment Questionnaire (CLINHAQ). The CLINHAQ was administered at each clinic visit^{2,16}. As of 2000, this instrument contains self-reports for the HAQ disability index^{17,18}, Arthritis Impact Measurement Scales (AIMS) anxiety and depression index¹⁹, VAS pain, VAS global severity, VAS gastrointestinal (GI) symptoms, VAS sleep problems, VAS fatigue, satisfaction with health, patient estimate of health status, and work ability. In 1996, questions relating to work ability were deleted and the helplessness subscale [Arthritis Helplessness Index (AHI)] of the Rheumatology Attitudes Index was added²⁰. In the current study we do not use the AHI, GI, health status, and health satisfaction scales.

The specific fatigue assessment used a double-anchored VAS labeled on one end, "Fatigue is no problem" and on the other end, "Fatigue is a major problem." The question read "How much of a problem has fatigue or tiredness been for you IN THE PAST WEEK?" The range of the scale is 0-3. The specific questions and anchors for the other VAS scales were on pain: "How much pain have you had because of your illness in the past week?" (no pain, severe pain); global severity: "Considering all of the ways that your illness affects you, rate how you are doing by placing a mark on the line" (very well, very severe); "How much problem has sleep (i.e., resting at night) been for you in the past week?" (sleep is no problem, sleep is a major problem).

The joint count was a count of 24 tender joints, assessing metacarpophalangeal (MCP), proximal interphalangeal (PIP), and metatarsophalangeal (MTP) joints as a single joint group. Positive MCP, PIP, or MTP joint groups were scored as 2 joints. Joints reported here included PIP, MCP, wrist, elbows, shoulders, hips, knees, ankles and MTP of the feet. The range of joint counts in this study was 0-24. Grip strength was assessed using the folded blood pressure cuff method²¹.

The Westergren ESR was measured by standard methodology²². Rheumatoid factor was determined by the Latex method. Methods in use in this clinic for these items have been reported^{23,24}.

Treatment related variables. At each clinic visit it was determined whether a patient was taking a DMARD and whether a new DMARD had been started. Also, we noted whether prednisone was being taken or if it had been started at the current clinic visit. A sequential count of the number of DMARD was also obtained. The following DMARD were assessed: methotrexate, azathioprine, hydroxychloroquine, injectable gold, auranofin, cyclosporine, minocycline, sulfasalazine, penicillamine, etanercept, and leflunomide.

Statistical Methods

Definition for an increase in treatment intensity. Treatment intensity was considered to increase if: (1) the number of DMARD increased from the previous visit (this definition included patients taking and not taking DMARD at the previous visit); or if (2) a change from one DMARD to another occurred. We also performed separate analyses considering that the addition of prednisone was also an increase in treatment intensity. Analyses did not indicate a significant additional contribution from prednisone. Therefore, for clarity of purpose, we restricted the analyses to increase in DMARD intensity.

To determine the strength of the association between individual clinical predictor variables and treatment changes, a series of regression analyses were performed using generalized estimating equations (GEE), as displayed in Table 2. Stata's implementation of the GEE procedure (Stata XTGEE) is an extension of generalized linear models (GLM) that properly handle panel data²⁵. In our analyses we used the Huber/White/sandwich estimator of variance. This estimator produces consistent standard errors even if the within-group correlations are not as hypothesized by the specified correlation structure²⁵. We also used as a covariate the total number of DMARD the patient had received. Multivariate associations were also assessed by GEE procedure, but in a logistic regression model.

In parallel analyses we used a tree-based modeling system (CART) to explore predictive variables that might not be disclosed by the more linear regression modeling^{25,26}. CART performs better than conventional logistic regression when the data contain nonlinear features, collinearity, and interactions. In using these analyses we sought to understand whether factors not disclosed by regression might be important in the decision to start DMARD therapy. CART analyses can be used when there is missing data because CART identifies surrogate variables that can be substituted when a variable is missing.

An observation not associated with a treatment change was scored as 0, and one in which a treatment change occurred was scored as 1. Because treatment changes occurring at the very first clinic visit might be associated with unusual circumstances, such visits were excluded from analysis.

RESULTS

Table 1 shows the average characteristics of the RA patients in this study. At the last observation the average disease duration was 12.2 [standard deviation (SD) 9.9] years (range 0.08–63.3). The average age of each patient during the course of the study was calculated, and an overall mean for all patients of 57.6 (SD 14.4) years was determined. Eighty-five (85.0%) percent were rheumatoid factor positive, and 78.1% were women. By the end of the study 78.8% of

patients had taken at least one DMARD. Among patients taking DMARD, the average number taken was 2.3 and the range was one to 9. Forty-six (46.2%) percent had used prednisone by the time of study closure.

Regression analyses. Table 2 shows the associations between change in therapy and clinical status variables. The coefficients represent the average difference in the clinical variable between those observations in which a new DMARD was started and the observations when therapy was continued without change. For example, change in DMARD status is associated with an increase of roughly 9 units in the ESR. The standardized coefficient presents this change in SD units, allowing comparison among predictors. The z score can be considered an overall measure of the predictive ability of the variable, since it considers both the standardized coefficient and the variability (standard error) of the coefficient. In agreement with van der Heijde, joint count, global severity, and ESR are the best predictors of DMARD change, along with global severity. Pain and global severity are highly correlated — $r = 0.75$, and they are about equally effective as predictors. In agreement with the ACR “core set,” we identified as important those variables used in the ACR index.

A second set of variables that contribute to prediction, though not as well, are grip strength, HAQ, depression, anxiety, morning stiffness, fatigue, sleep disturbance, and helplessness.

In multivariate analyses we were unable to add HAQ to the model because of colinearity with pain and global severity. When HAQ was omitted from the model, the “best” multivariate model was painful joint count, VAS pain, ESR, global severity, and younger age; other variables were not significant in the model and global severity had the weakest effect owing to its colinearity with pain. Neither the number of previous DMARD, date (reflecting the availability of new DMARD), nor duration of disease were significant predictors of DMARD change.

Classification tree analyses. Regression models allow one

Table 1. Mean and percentile values of clinical status variables for 1905 patients with RA.

| Variable | N | Mean | SD [†] | 0th | 25th | 50th | 75th | 100th |
|------------------------|--------|--------|-----------------|-------|-------|-------|--------|--------|
| Joint count, 0–24 | 26,114 | 7.55 | 5.87 | 0.00 | 2.00 | 7.00 | 12.00 | 24.00 |
| Pain, 0–3 | 17,211 | 1.38 | 0.78 | 0.00 | 0.70 | 1.40 | 2.00 | 3.00 |
| Global severity, 0–100 | 25,526 | 43.81 | 24.02 | 0.00 | 25.00 | 50.00 | 60.00 | 100.00 |
| ESR, mm/h | 21,605 | 34.24 | 25.13 | 0.00 | 15.00 | 30.00 | 47.00 | 147.00 |
| Grip strength, mm/Hg | 25,856 | 113.36 | 56.34 | 30.00 | 75.00 | 99.00 | 136.00 | 300.00 |
| HAQ, 0–3 | 23,602 | 1.31 | 0.77 | 0.00 | 0.75 | 1.25 | 1.88 | 3.00 |
| Depression, 0–10 | 20,597 | 2.39 | 1.73 | 0.00 | 0.99 | 1.98 | 3.30 | 9.90 |
| Anxiety, 0–10 | 20,489 | 3.45 | 1.98 | 0.00 | 1.90 | 3.30 | 4.90 | 9.90 |
| AM stiffness, 0–8 | 25,843 | 2.36 | 4.47 | 0.00 | 0.20 | 1.00 | 2.00 | 24.00 |
| Fatigue, 0–3 | 6694 | 1.57 | 0.86 | 0.00 | 0.80 | 1.60 | 2.30 | 3.00 |
| Sleep disturbance, 0–3 | 6662 | 1.20 | 0.89 | 0.00 | 0.40 | 1.00 | 2.00 | 3.00 |

[†]Overall standard deviation (between-patient SD and within-patient SD).

Table 2. Difference in clinical variables as a function of whether a new DMARD was started*.

| Variable | Coefficient | SE | Z Score | p | Standardized Coefficient |
|------------------------|-------------|------|---------|---------|--------------------------|
| Joint count, 0–24 | 2.82 | 0.12 | 22.67 | < 0.000 | 0.48 |
| Pain, 0–3 | 0.35 | 0.02 | 18.40 | < 0.000 | 0.45 |
| Global severity, 0–100 | 9.60 | 0.52 | 18.35 | < 0.000 | 0.40 |
| ESR mm/h | 8.96 | 0.56 | 15.91 | < 0.000 | 0.36 |
| Grip strength, mm/Hg | -11.89 | 0.85 | -13.97 | < 0.000 | -0.21 |
| HAQ, 0–3 | 0.17 | 0.01 | 12.72 | < 0.000 | 0.23 |
| Depression, 0–10 | 0.46 | 0.04 | 12.33 | < 0.000 | 0.26 |
| Anxiety, 0–10 | 0.42 | 0.04 | 11.17 | < 0.000 | 0.21 |
| AM stiffness, 0–8 | 1.32 | 0.13 | 10.33 | < 0.000 | 0.29 |
| Fatigue, 0–3 | 0.20 | 0.03 | 7.43 | < 0.000 | 0.24 |
| Sleep disturbance, 0–3 | 0.23 | 0.03 | 6.83 | < 0.000 | 0.26 |

*Controlling for the number of previous DMARD.

to identify linear models, but do not do well with interactions, colinearity, and nonlinearity. For that reason we explored the same set of analyses using CART, a classification tree analysis method. The strength of tree-based analysis is in the ability to identify distinct subsets with special characteristics. The most important predictors of DMARD change in these CART analyses were pain and tender joint count, with importance scores of 100 and 90.3, respectively (100 is maximum score). But other variables playing an important role (as splitters high on tree) were fatigue and sleep disturbance (Figure 1). Additional splitters were ESR, number of previous DMARD, grip strength, anxiety, duration, and age. These data indicate that the identification of predictor variables is more complex and variable than the ordinary logistic models would suggest. Somewhat unexpectedly, HAQ was not identified in the CART analyses. To be certain that this was not an artifact of missing data, we excluded all observations in which HAQ was missing and then re-ran the analyses. HAQ was still not identified in the CART models.

DISCUSSION

This study, as with the van der Heijde study, does not test which variables are most associated with disease activity. Instead, it tests which variables are most associated with a change in treatment. There is a presumption that therapy is changed primarily because of disease activity, but this has not been proven. Therapeutic decisions might reflect physician beliefs (e.g., the importance of the joint count compared to the HAQ score) or the intensity of patient complaints. It is of some interest that the HAQ, clearly the best predictor of longterm outcomes, plays a limited role in predicting treatment change, while pain, global severity, and joint count, much poorer predictors of longterm outcome, play a much more prominent role in treatment change.

One apparent explanation for these observations is that the physician reacts to pain, global severity, and joint activity, which are immediately obvious during the patient interview and physical examination. Similarly, the ESR (available in this study to the examiner at the time the patient was seen in clinic) plays a role as a “known” identi-

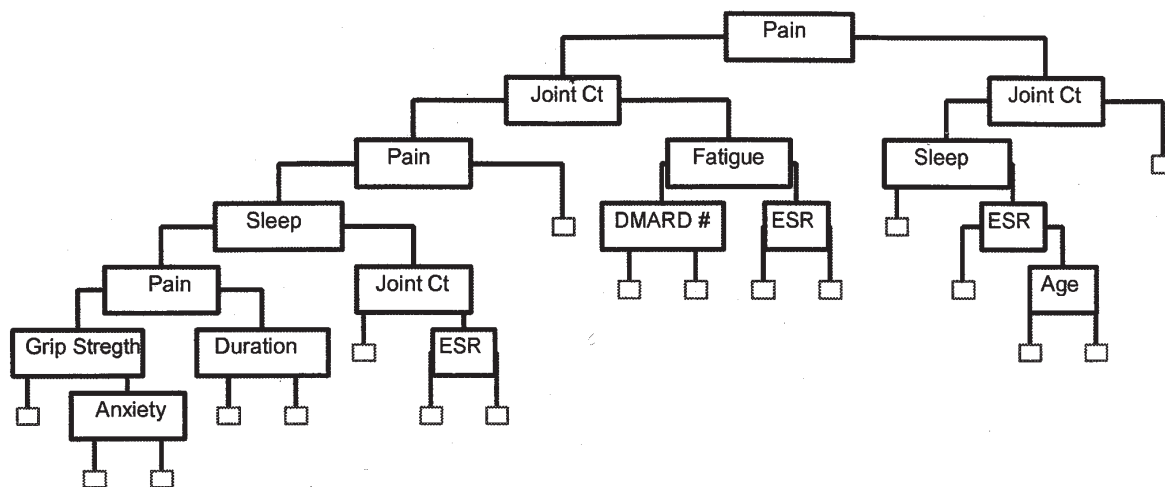


Figure 1. Classification tree for the prediction of DMARD start. Pain and tender joint count are the most important variables. A second tier of variables includes fatigue, sleep, and ESR. HAQ does not appear as a predictor in these analyses.

fier of disease activity. The other measures, change in function, amount of fatigue, and sleep disturbance, are not as clearly known, nor is the interpretation of such scales as clearly understood. It is therefore possible that these measures are better predictors of disease activity than is indicated by this report.

If it is true that it is primarily pain, severity, and joint abnormality that are important in detecting disease activity in a clinical setting, this fact may explain why questionnaires are not used as often as advocates urge, i.e., that pain, global severity, and joint abnormality may be quite obvious to the clinician even without formal assessment. As we have noted above, there are no studies that shed light on whether formal assessment adds usefully to the informal assessment that is more commonly provided.

As we noted above, one reason to make formal measurements is to provide documentation to third parties about the appropriateness of treatment and to demonstrate the effect of treatment. This report extends the observations of van der Heijde and associates to RA of varying durations, and confirms the utility of the assessments advocated in the ACR core set. In the current report we used a shortened version of the modified Ritchie index, one that was effective and could be performed quickly in the clinic. We therefore suggest that a minimum set of evaluation should comprise a joint count, ESR or CRP, measures of pain and/or severity, a fatigue scale (fatigue being a surrogate for sleep disturbance), and a measure of function such as the HAQ¹⁷ or MHAQ²⁷. Simple assessment tools like the Arthritis and Lifestyle Index, the MDHAQ²⁸, or the CLINHAQ^{2,29} are readily available for such purposes.

This study also adds insight into the very difficult question of how severe arthritis must be for DMARD therapy to be instituted or changed. Table 3 indicates that in actual practice many patients with relatively low disease activity scores will, and we believe should, receive DMARD therapy. An easy way to assess this is with a rule of thumb: patients with scores at the 20th percentiles or above should always receive DMARD therapy, and patients with scores below that level should receive therapy if so desired. As part

of this symposium, we have published percentile charts for patients with RA, and these charts may be used as an easy way to assess severity and results of therapy³⁰.

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Table 3. Mean and percentile values of clinical variables at the start of a new DMARD.

| Variable | N | Mean | SD | 0th | 25th | 50th | 75th | 100th |
|------------------------|------|--------|-------|-------|-------|-------|--------|--------|
| Joint count, 0–24 | 2197 | 10.23 | 5.99 | 0.00 | 6.00 | 10.00 | 15.00 | 24.00 |
| Pain, 0–3 | 1462 | 1.72 | 0.78 | 0.00 | 1.20 | 1.90 | 2.30 | 3.00 |
| Global severity, 0–100 | 2181 | 53.01 | 24.64 | 0.00 | 33.00 | 50.00 | 72.00 | 100.00 |
| ESR, mm/h | 1662 | 41.97 | 27.74 | 0.00 | 20.00 | 37.00 | 60.00 | 140.00 |
| Grip strength, mm/Hg | 2168 | 102.40 | 50.99 | 30.00 | 69.00 | 90.00 | 120.00 | 300.00 |
| HAQ, 0–3 | 2005 | 1.48 | 0.74 | 0.00 | 1.00 | 1.50 | 2.00 | 3.00 |
| Depression, 0–10 | 1730 | 2.83 | 1.89 | 0.00 | 1.32 | 2.60 | 3.90 | 9.20 |
| Anxiety, 0–10 | 1724 | 3.88 | 2.07 | 0.00 | 2.30 | 3.90 | 5.28 | 9.90 |
| AM stiffness, 0–8 | 2181 | 3.65 | 5.67 | 0.00 | 0.50 | 1.70 | 4.00 | 24.00 |
| Fatigue, 0–3 | 606 | 1.77 | 0.84 | 0.00 | 1.10 | 2.00 | 2.40 | 3.00 |
| Sleep disturbance, 0–3 | 603 | 1.45 | 0.95 | 0.00 | 0.60 | 1.50 | 2.30 | 3.00 |

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