Which Variables Best Predict Change in Rheumatoid Arthritis Therapy in Daily Clinical Practice?

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ABSTRACT. ***Objective.*** To determine in clinical practice which clinical status variables for rheumatoid arthritis (RA) are most closely associated with a change in disease modifying antirheumatic drug (DMARD) therapy.

Methods. A prospective monocenter study was conducted in 204 consecutive patients with RA. Rheumatologists recorded patient characteristics, treatments, and disease activity data [tender and swollen joint count (28), morning stiffness, visual analog scale (VAS) for pain (0–100 mm), patient global assessment and physician global assessment, Westergren erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)]. The rheumatologists decided whether or not to initiate or change treatment but were not informed that their decisions were part of the investigation. Logistic regression analysis was performed to evaluate which study variables best predict change in therapy. ROC analysis was used to obtain the cutoff value of the different composite indices ($DAS_{28(ESR)}$, $DAS_{28(CRP)}$, SDAI) for treatment change, as well as sensitivity and specificity.

Results. The variables that were predictive for a change in treatment were (in descending order): swollen joint count, morning stiffness, CRP, tender joint count, and patient global assessment. Composite index values associated with a decision to modify DMARD therapy were: $DAS_{28(ESR)}$ 4.2 (sensitivity 87%, specificity 70%); $DAS_{28(CRP)}$ 3.6 (sensitivity 86%, specificity 78%); and SDAI 15 (sensitivity 90%, specificity 86%). The discriminative ability of SDAI was better than that of $DAS_{28(CRP)}$ or $DAS_{28(ESR)}$.

Conclusion. In our study, swollen joint count was the variable with the greatest weight, which explains the observed better performance of SDAI. (First Release April 15 2006; J Rheumatol 2006;33:1243–6)

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The goal of medical treatment in rheumatoid arthritis (RA) is to obtain a state of low disease activity and, if possible, a state of remission, in order to minimize structural damage and improve functional status[1]. For assessment of disease activity in daily clinical practice, the Disease Activity Score with reduced joint count (DAS28) or the Simplified Disease Activity Index (SDAI) can be used[2,3]. The DAS28 ($DAS_{28(ESR)}$) is a continuous measure that includes (in order of importance): 28 tender joint count, erythrocyte sedimentation rate (ESR), 28 swollen joint count, and general health based on 100 mm visual analog scale (VAS)[2]. $DAS_{28(ESR)}$ is a continuous measure with a theoretical range from 0 to 10. A score above 5.1 on $DAS_{28(ESR)}$ indicates high disease activity and a score below 3.2 indicates low disease activity[2]. Recently, DAS28 formulae were developed using C-reactive protein (CRP) instead of ESR ($DAS_{28(CRP)}$)[4].

The SDAI is the numeric sum of 5 outcome variables: tender and swollen joint count (based on a 28-joint assessment), patient and physician global assessment of disease activity (VAS 0–100 mm), and CRP (mg/dl, normal < 0.5 mg/dl)[3]. SDAI was validated by analysis of the leflunomide database of patients with active RA. Findings from survey cases indicate levels of disease activity: SDAI > 40 = high disease activity; 20–40 = moderate RA activity; and < 20 = mild disease activity[3]. In a more recent article by Aletaha, *et al*, however, the criteria for defining disease activity rates were considerably different[5].

The aim of our study was to determine which variables best predict a change in RA therapy in daily clinical practice. The cutoff values associated with a change in disease modifying antirheumatic drug (DMARD) for the $DAS_{28(ESR)}$, $DAS_{28(CRP)}$, and SDAI were also determined.

MATERIALS AND METHODS

Patients and variables assessed. We conducted a prospective monocenter study at Cochin Hospital, a tertiary care center, between January and April 2004. A total of 204 consecutive outpatients fulfilling American College of Rheumatology (ACR) criteria for RA were evaluated. During a visit, a standardized information sheet was filled out. A thorough survey of records of

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each patient, from disease onset, also included disease duration, rheumatoid factor positivity, current and previous DMARD, and total and daily dose of corticosteroids. RA structural status, evaluated using the last available radiographs of hands and feet (< 2 years before the visit), classified patients according to binary response as erosive versus non-erosive. Disease activity was assessed in each patient based on: tender and swollen joint count (out of 28), morning stiffness, VAS for pain (0–100), patient global assessment, physician global assessment (0-100 VAS), and last value obtained for Westergren ESR and CRP. We did not calculate $DAS_{28(ESR)}$, $DAS_{28(CRP)}$, or SDAI during the visit. The Health Assessment Questionnaire was not included since it is not recommended in France for management of RA in daily clinical practice[6]. An additional question recorded on the sheet at examination of each patient was the decision of the rheumatologist (DZ, LG, XA, CR, MD) to initiate or change DMARD. The rheumatologists were not informed that their decisions were part of the investigation. Concealment was possible because at the same time the patients were taking part in a prospective study on lipid metabolism in RA[7].

Statistical analysis. The demographic and disease activity variables of the patients were compared with regard to the rheumatologist's decision whether or not to change DMARD therapy (i.e., modify ongoing therapy or initiate another DMARD). In order to evaluate the relative weight of the variables with regard to the rheumatologist's decision, independent variables were identified by univariate analysis in which the dependent variable was the rheumatologist's decision to change DMARD therapy. We then conducted a multivariate logistic regression analysis to identify the variables that were independently associated with the decision to change DMARD therapy. Standardized beta coefficient and corresponding odds ratio were used because they allow comparison of predictors. To determine the cutoff value according to $DAS_{28(ESR)}$, $DAS_{28(CRP)}$, and SDAI, receiver operating characteristic (ROC) curves were constructed. ROC curves serve to plot relationships between sensitivity and specificity for the different levels of testing and are constructed using index values for each patient. The area under the curve (AUC) provides a measure of overall discriminative capacity of a model as a basis for calculating the cutoff value with higher sensitivity and specificity. To calculate this value we obtained the sums of sensitivity and specificity and chose the highest one. Data were analyzed using SAS (version 8) software.

RESULTS

Clinical and demographic characteristics of study population. Study rheumatologists decided to change the current DMARD or to initiate a new DMARD in 94 of the 204 recruited patients. The characteristics of the 110 patients who had no change in treatment versus the 94 patients whose treatment was changed are summarized in Table 1. Mean age was lower in the patients whose treatment was changed. There was no statistical difference between the 2 groups in disease duration, presence of erosions, rheumatoid factor, mean number of previous DMARD, or use of corticosteroids. However, the mean dose of corticosteroids was higher in the patients whose treatment was changed. As expected, those in whom the treatment was changed had more active disease, as evaluated by the following: morning stiffness, pain, patient global assessment, physician global assessment, tender and swollen joint count, ESR, CRP, $DAS_{28(ESR)}$, $DAS_{28(CRP)}$, and SDAI.

Candidate variables for predicting change in DMARD were the following clinical variables (duration of morning

Table 1. Characteristics of 204 patients with RA grouped according to DMARD therapy status: 110 patients for whom DMARD treatment was not changed (Stable Group) and 94 patients for whom DMARD treatment was changed (Change Group). Values are mean ± SD, except where otherwise indicated.

	Stable Group, n = 110	Change Group, n = 94	p
Age, yrs	58 ± 14	53 ± 14	0.017
Sex: female, no. (%)	93 (85)	76 (81)	0.57
Disease duration, yrs	14 ± 10	12 ± 10	0.07
Positive RF, no. (%)	83 (75)	68 (72)	0.63
Bony erosions, no. (%)	101 (92)	79 (84)	0.12
No. of previous DMARD	2.7 ± 1.8	2.8 ± 2.0	0.85
Concomitant treatment			
Concomitant corticosteroids, no. (%)	65 (59)	60 (64)	0.56
Corticosteroid dose, mg/day	4.2 ± 3	5.4 ± 4	0.03
Concomitant TNF-α blockers, no. (%)	52 (47)	30 (32)	0.03
Disease severity characteristics			
Morning stiffness, min	8 ± 19	75 ± 97	< 0.0001
Tender joint count†	1.3 ± 2.0?	5.3 ± 5.0	< 0.0001
Swollen joint count†	2.6 ± 2.7	7.6 ± 4.0	< 0.0001
VAS for pain, 0–100 mm	21 ± 22	49 ± 24	< 0.0001
Patient global assessment, 0–100 mm VAS	23 ± 20	54 ± 23	< 0.0001
Physician global assessment, 0–100 mm VAS	17 ± 15	49 ± 17	< 0.0001
ESR, mm/h	18 ± 13	28 ± 21	< 0.0001
CRP, mg/l	6.4 ± 6.1	17.6 ± 19.9	< 0.0001
$DAS_{28\ (ESR)}$	2.89 ± 1.00	4.73 ± 1.18	< 0.0001
$DAS_{28\ (CRP)}$	2.67 ± 0.84	4.44 ± 1.08	< 0.0001
SDAI	8.51 ± 5.92	25.0 ± 10.5	< 0.0001

† 28-joint counts. RF: rheumatoid factor; DMARD: disease modifying antirheumatic drugs; TNF-α: tumor necrosis factor-α; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS: Disease Activity Score; SDAI: Simplified Disease Activity Index.

stiffness, pain, patient global assessment, tender joint count, and swollen joint count), acute phase reactants (ESR, CRP), and treatment (mean dose of corticosteroid) (Table 2). There was a negative correlation with age and tumor necrosis factor-α blocker treatment (Table 3).

Table 2. Variables predictive of change in DMARD treatment in RA: univariate analysis.

	OR	95% CI	p
Morning stiffness	1.03	1.02–1.04	< 0.001
Pain	1.04	1.03–1.06	< 0.001
Disease activity (patient)	1.06	1.04–1.07	< 0.001
Tender joint count	1.54	1.33–1.78	< 0.001
Swollen joint count	1.42	1.28–1.57	< 0.001
ESR	1.03	1.01–1.05	< 0.001
CRP	1.10	1.01–1.05	< 0.001
Corticosteroid dose, mg/day	1.09	1.00–1.20	0.04
Age	0.98	0.96–0.99	0.027
Anti-TNF-α	0.52	0.29–0.93	0.025

Table 3. Variables predictive of change in DMARD treatment in RA: multivariate analysis.

	Standardized ß Coefficient	Standardized Odds Ratio
Swollen joint count	1.657	5.24
Morning stiffness	1.218	3.38
CRP	1.030	2.8
Tender joint count	0.985	2.67
Patient global assessment	0.864	2.37
Pain	–0.013	0.98
ESR	–0.3234	0.72
Anti-TNF-α	–0.436	0.64
Age	–0.394	0.67
Corticosteroid dose, mg/day	–0.131	0.87

In terms of contributing to change in DMARD therapy, swollen joint count was the most predictive variable; morning stiffness was second; overall, CRP and the tender joint count had the same weight; and the least predictive was patient global assessment.

ROC curves and cutoff values. The ROC curves of $DAS_{28(ESR)}$, $DAS_{28(CRP)}$, and SDAI are shown in Figure 1. The discriminative ability of SDAI was better than that of $DAS_{28(CRP)}$ or $DAS_{28(ESR)}$. This ability can also be seen by comparing the AUC data in Table 4. The optimal cutoff points that corresponded with treatment changes were as follows: $DAS_{28(ESR)}$ 4.2 (sensitivity 87%, specificity 70%); $DAS_{28(CRP)}$ 3.6 (sensitivity 86%, specificity 78%); and SDAI 15.1 (sensitivity 90%, specificity 86%).

DISCUSSION

The decision to change DMARD treatment is made when the rheumatologist considers that control of disease activity is not sufficient. It is widely accepted that tight control of disease activity is associated with less structural damage and better functional outcome[1,8,9]. In our study, swollen joint count, morning stiffness, tender joint count, CRP, and patient global

Table 4. Area under the curve of the ROC curves for decision to change DMARD, and cutoff values.

	AUC (95% CI)	Optimal Cutoff	Sensitivity, %	Specificity, %
SDAI	0.923 (0.895–0.965)	15	90	86
$DAS_{28\ (CRP)}$	0.902 (0.861–0.943)	3.6	86	78
$DAS_{28\ (ESR)}$	0.872 (0.831–0.925)	4.2	87	70

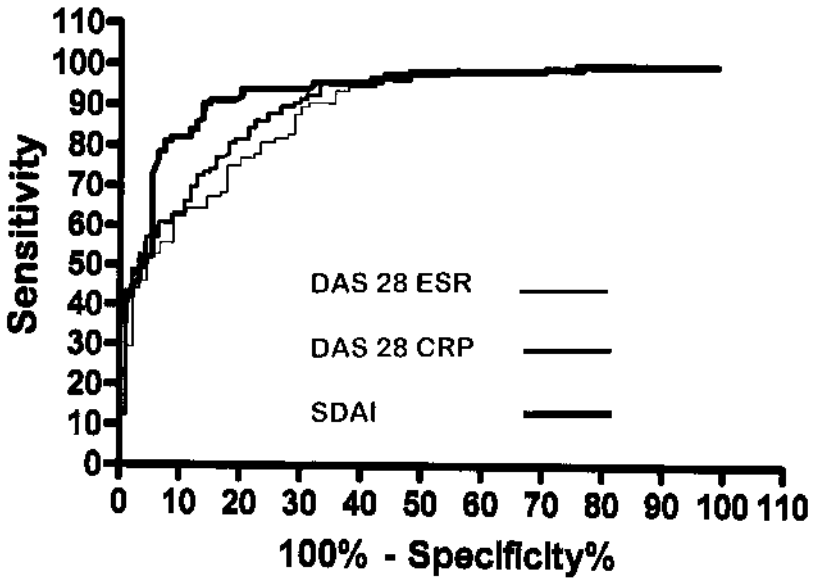

Figure 1. ROC curves of $DAS_{28(ESR)}$, $DAS_{28(CRP)}$, and SDAI.

assessment were predictive of change in DMARD. Conversely, the most important determinants of DAS were (in descending order): tender joint count, ESR, swollen joint count, and patient global assessment[2].

The greater importance accorded to synovitis in our study may be explained by increasing knowledge of an association between presence of synovitis and structural damage. Wolfe, using a different approach, reached the same conclusions[10,11]. The agreement of DAS28 with physician assessment of RA activity was determined in 669 consecutive RA patients from the practices of 61 Canadian and US rheumatologists. The patients were assessed using DAS28, and physician assessment of RA activity was performed using an 11-point predefined scale. The level of agreement was low. Indeed, among patients with DAS28 > 5.1, 14.2% had mildly active RA, 60.2% had moderate activity, and 25.7% had severe disease activity according to the physician assessment. In Wolfe's opinion, DAS28 rated disease activity higher than physician assessment because DAS28 is sensitive to tender joint count and ESR and because, as in our study, physician assessment was based mainly on the swollen joint count[10].

The greater importance accorded to CRP in our study may be explained by the fact that suppression of CRP is associated with a decrease in radiographic progression and improvement in functional score[12,13]. That less importance is given to ESR is not surprising, since ESR can be influenced by confounding factors such as age, gender, fibrinogen levels, hyperglobulinemia, rheumatoid factor, and anemia. Morning stiffness is not a parameter of DAS28 nor of the ACR core set. Morning stiffness is the clinical manifestation of persistent inflammation, which is probably why it has acquired such importance in the decision to change DMARD therapy.

The desirability of a low CRP explains why the $DAS_{28(CRP)}$ cutoff value was lower than that of $DAS_{28(ESR)}$. The cutoff value of SDAI was 15, and SDAI had the highest sensitivity and specificity. The discriminative ability of SDAI was better than that of $DAS_{28(CRP)}$ or $DAS_{28(ESR)}$ because in the SDAI a similar weight is given to swollen and tender joint counts.

The cutoff values were close to the thresholds of moderate activity defined by Aletaha, *et al*[5]. Thus, to distinguish remission, low, moderate, and high disease activity, they applied as criteria DAS28 scores of 2.4, 3.6, and 5.5, and SDAI scores of 3.3, 11, and 26, respectively.

Our findings should be evaluated in other sets of patients and, if confirmed, should prompt reappraisal of current recommendations for initiating anticytokine therapy both in clinical trials and in daily practice[14].

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