

## EXTENDED REPORT

## Applying low disease activity criteria using the DAS28 to assess stability in patients with rheumatoid arthritis

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**Objectives:** To examine whether low disease activity criteria using the disease activity score (DAS28) can be applied to identify a reasonably large number of patients with stable low disease activity of rheumatoid arthritis (RA) over a six month period, with the ultimate intention of including these patients in a substitution based, shared care model. Additionally, to assess the reliability of the DAS28 for selecting patients with stable disease from an outpatient population.

**Methods:** Patients regularly seen at the rheumatology outpatient department of the university hospital Maastricht, were invited for assessment of the stability of their RA. The shared care model was intended to provide care to patients with stable, low disease activity of RA by nurse specialists. For this, patients underwent assessments using the DAS28 criteria at entry and three and six months later. Test-retest reliability was assessed for composing measures as well as for the DAS28.

**Results:** Of the 97 outpatients included, one third (31 patients) did not complete the study. Patients with missing data were older and assessed their disease activity as greater than patients with complete data. Applying the low disease activity criteria to assess stability over a period of six months ( $\text{DAS28(T0)} \leq 3.2$  and  $\text{DAS28(T6)} - \text{DAS28(T0)} \leq 1.2$ ) resulted in identification of 22/56 (39%) patients with stable, low disease activity of RA. A good similarity score (intraclass correlation coefficient=0.82) for the DAS28 was found.

**Conclusions:** The low disease activity criteria using the DAS28 can be used to select patients with stable, low disease activity of RA from a rheumatic outpatient population.

Recently, different new models of organising care for patients with chronic disease have been introduced to optimise the treatment of the growing number of chronically ill people in Western countries.<sup>1</sup> In the care of patients with medically stable chronic disease, medical specialists can allocate activities to other health professionals, allowing the specialists to divert their attention towards managing patients with more “serious” problems.<sup>2–4</sup> Stable in this context means constant low activity of the chronic disease—that is, without flares. These substitution based models are believed to be better approaches to planning and delivering health care to chronically ill patients.<sup>5</sup>

In rheumatoid arthritis (RA) the concept and definition of stability is more troublesome than in chronic diseases like diabetes mellitus or chronic obstructive pulmonary disease. The activity of RA cannot be simply expressed by one single parameter and the presentation of RA may vary substantially over time between patients as well as within the same person, considering the not uncommon occurrence of flares.<sup>6</sup> Nevertheless, for RA too—a chronic disease for which the number of patients is predicted to rise—substitution based models of care are gaining interest.<sup>5,7</sup>

Disease stability is derived from measurements of disease activity, which have a central place in the management of RA because reducing disease activity is the paradigm of treatment of RA. Measures of rheumatic disease activity can be classified as both process and outcome measures.<sup>8</sup> Kirwan defined process as “the abnormal physiological consequences that follow from the cause of the disease” and outcome as “the suffering or loss of health (death, disability, discomfort, iatrogenic, economic) of the patient caused by the disease process”.<sup>8</sup> Agreement on which measurements to include in assessing disease activity in RA has been reached both in Europe (European League Against Rheumatism (EULAR) core set) and in America (American College of Rheumatology (ACR) core set).<sup>9</sup>

Notwithstanding the consensus about which end points to measure when assessing disease activity (both core sets comprise process measures), the definition of rheumatic stability, as derived from subsequent measurements of rheumatic activity, still varies. Disease stability can be defined as the lack, within certain limits, of changes or fluctuations in parameters of a disease within a defined period of time. To assess disease stability a time component has to be included in the measure: based on subsequent measures of disease activity, the degree of disease stability can be assessed.

From the EULAR core set the so-called EULAR response criteria were derived, while criteria for improvement have been developed based on the ACR core set. The latter define change as a difference of 20% or more in subsequent measurements of tender and swollen joint counts and a difference of 20% or more in at least three out of five remaining measures.<sup>10</sup> The EULAR response criteria make use of a disease activity score (DAS28) derived from four measures and, in addition to change in disease activity from baseline, also take the level of disease activity attained during follow up into account when defining response.<sup>6,11</sup> When these definitions are considered within the context of assessing stability in this study, then low disease activity at baseline is also necessary. Otherwise, patients with severe RA are classified as having stable, low disease activity of RA and consequently not managed adequately. Thus, only the EULAR response criteria seem to be applicable in this case to assess stability, although they were not originally developed for this purpose. Although the use of these criteria to include patients has been advocated previously,<sup>6</sup> no study has yet reported the results of this particular application.

**Abbreviations:** ACR, American College of Rheumatology; DAS28, disease activity score; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis

**Table 1** Baseline characteristics of patients with complete measurements and of patients with missing measurements. Results are given as mean (SD) unless stated otherwise

Characteristic	Complete measurements (n=66)	Missing measurements (n=31)	p Value
Age (years)	62.7 (12.4)	68.6 (11.9)	0.030*
Sex (No (%) male)	29 (44)	17 (55)	0.316†
Tender joints	2.7 (3.2)	3.9 (4.4) [27]	0.165*
Swollen joints	3.3 (3.1)	4.1 (2.9) [28]	0.275*
ESR (mm/1st h)	18.3 (17.0) [63]	24.5 (25.0) [27]	0.176*
Global DA§	3.0 (1.0) [62]	3.5 (0.9) [24]	0.035*
DAS28	2.9 (1.0) [63]	3.5 (1.0) [22]	0.050‡

Numbers in square brackets are the number of patients for whom data are available when case data were not available for the whole group.

\*Student's *t* test; †Pearson  $\chi^2$ ; ‡Mann-Whitney U test; §global assessment of disease activity.

This study examines whether low disease activity criteria using the DAS28 can be applied to identify a reasonably large number of patients with a stable low disease activity of RA over a six month period, with the ultimate intention of including these patients in a substitution based, shared care model.

## PATIENTS AND METHODS

### Patient selection

All patients who were receiving care by rheumatologists at the rheumatology outpatient department of the University Hospital Maastricht and known to have RA, according to the criteria of the ACR,<sup>12</sup> were identified.

An explanatory letter with informed consent form and postage-free envelope were mailed to patients with RA. Only those patients were invited who had been referred by general practitioners willing to have a rheumatology nurse in their practice if the model were implemented in clinical practice after completion of this feasibility study. After having given their informed consent, patients were scheduled for assessment of disease activity by a rheumatology nurse in the outpatient department of the hospital. Three assessments were scheduled: at entry (T0), and three months (T3) and six months later (T6). Just before every assessment patients were sent a self report form and asked to complete this on the day of assessment and return it to the nurse. Three months was chosen as the interval between measurements of stability because this period of time is used by many doctors when seeing patients with stable chronic disease. Assessments were performed between April 1998 and February 1999.

### Measures of disease activity

The number of swollen and the number of tender joints were both assessed by 28 joint counts.<sup>13</sup> For this a mannequin, consisting of a stick figure drawing of a person with each joint indicated by a circle, was used. The rheumatology nurses marked the tender or swollen joint by ticking the appropriate circle (range 0–28). A five point Likert scale (1 = asymptomatic; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe)

was used for global assessment of disease activity by the patient.<sup>14</sup> Blood samples were taken to determine the Westergren erythrocyte sedimentation rate (ESR). The DAS28 was calculated from the ESR, number of tender and swollen joints assessed by the nurse, and the patient's global assessment of disease activity.<sup>6, 11, 15</sup> This score may range from 0 to 9.3, where a DAS28 score  $\leq 3.2$  is considered to reflect low disease activity and a DAS28 score  $> 5.1$  high disease activity.<sup>11</sup>

### Stability criteria

When the DAS28 is applied to define low and stable disease activity, patients are classified as having stable RA if at baseline the DAS28 was  $\leq 3.2$  (low current disease activity) and the difference in DAS28 scores between baseline and the last measurement was  $\leq 1.2$ . This difference is twice the measurement error and is considered to be a statistically significant change in disease activity.<sup>11</sup>

### Statistical analysis

Baseline comparisons between patients with and without complete data were performed with Student's *t* test, Pearson  $\chi^2$  test, and the Mann-Whitney U test. Test-retest reliability was assessed with the intraclass correlation coefficient (ICC), using the scores obtained at the three measurements.<sup>16</sup> The findings from the application of the DAS28 to assess stability were expressed as proportions.

Data processing and analyses were conducted with SPSS (Windows release 9.0).

## RESULTS

### Patients

One hundred and nine patients were eligible for the study, of whom 97 gave informed consent. Reasons for not giving informed consent were lack of interest (n=4) or unknown (n=8). After giving informed consent 66 patients (68%) completed the study. Thirty one patients (32%) dropped out because of loss of interest (n=9) or for unknown reasons (n=22).

**Table 2** Intraclass correlation coefficient (ICC) for measurements of activity

Measurement	N	Mean (SD)			Intraclass correlation coefficient§	95% CI
		T0*	T3†	T6‡		
Tender joints	65	2.8 (3.2)	3.2 (3.3)	3.4 (3.8)	0.74	0.61 to 0.83
Swollen joints	65	3.4 (3.1)	2.8 (2.9)	2.7 (3.0)	0.80	0.70 to 0.87
ESR (mm/1st h)	60	18.6 (17.4)	20.4 (19.2)	22.5 (17.6)	0.94	0.91 to 0.96
Global DA¶	62	6.4 (1.4)	6.5 (1.6)	6.4 (1.7)	0.86	0.79 to 0.91
DAS28	56	3.0 (1.0)	3.2 (0.9)	3.2 (1.1)	0.82	0.72 to 0.89

\*T0 measurement at start; †T3 measurement three months after start; ‡T6 measurement six months after start; § $p < 0.001$ ; ¶global assessment of disease activity.

**Table 3** Scores of patients on DAS28 at baseline, six months later, and differences between scores at baseline and six months later

T0*	T6-T0	T6†			Total
		≤3.2	>3.2 but ≤5.1	>5.1	
≤3.2	≤1.2	18	4	0	22
	>1.2	0	4	1	5
>3.2 but ≤5.1	≤1.2	11	15	0	26
	>1.2	0	1	0	1
>5.1	≤1.2	0	0	2	2
	>1.2	0	0	0	0
Total		29	24	3	56

\*T0 measurement at start; †T6 measurement six months after start.

Comparison of groups with and without data at all measurements showed a statistically significant difference, in that older patients with missing data on average reported a higher mean score for both global assessment of disease activity and DAS28 (table 1). The presence of data at all measurements does not imply complete data. Moreover, for 56 patients complete data were available, while for 10 patients the score on one or more variables at one or more measurements was absent.

**Reliability of measurements for stability assessment**

Assessment of reliability of measurements at baseline and at three and six months showed moderate ICCs (0.6–0.8) for tender and swollen joints assessed by the nurse (table 2). Good ICCs (>0.8–0.9) were found for global assessment of disease activity, and DAS28, while a very good ICC (>0.9) was found for ESR.

**Measuring disease stability**

Applying the DAS28 showed low disease activity in 27/56 (48%) patients at baseline (table 3). The difference in DAS28 between baseline and the last measurement was ≤1.2 for 50/56 (89%) patients. At T6 18/56 (32%) patients could be classified as having stable, low disease activity of RA, while 11 (20%) patients had changed from medium to low disease activity of RA.

Four patients with low disease activity of RA at baseline did not change more by than 1.2 DAS28 points but had medium disease activity of RA six months after baseline measurement.

Between baseline and measurement at three months 52/56 (93%) did not change by more than 1.2 DAS28 points, and between baseline and the last measurement at six months 50/56 (89%) patients did not change by more than 1.2 DAS28 points (table 4). When the allowed change was set at 0.6 (one times the measurement error), these proportions were 79%

(44/56) and 68% (38/56) respectively. Applying the low disease activity criteria, that is a DAS28 baseline score ≤3.2 and a difference ≤1.2 between DAS28 scores at baseline and the last measurement, resulted in stable low disease activity of RA in 22/56 (39) patients.

**DISCUSSION**

The disease activity of outpatients with RA was assessed on several occasions with the ultimate intention of including these patients in a shared care model. For this assessment, low disease activity criteria using the DAS28 were applied. The DAS28 is developed to measure a clinically relevant decrease in disease activity resulting from a treatment. In this study, however, the DAS28 was used for a different purpose—namely, to assess disease stability by defining stability as “the lack, within certain limits, of changes or fluctuations in parameters of a disease within a defined period of time”, where the “limits” were defined by the EULAR response criteria. Without the existence of a “gold standard” to assess stability in RA, interpretation of the findings of this study is not always unambiguous.

It was found that 22/56 (39%) patients could be classified as having stable, low disease activity of RA. The defined extent of change (1.2 DAS28 points) raises an important issue. A patient with an initial DAS28 of 3.2 at baseline and 4.4 at last follow up has, according to this change, stable RA while his/her index score increases between the first and last measurement by 37.5%. When the defined extent of change was 0.6 DAS28 points, 16 (29%) patients at T6 showed stable, low disease activity of RA. When applying the DAS28 baseline score at all measurements (DAS28(T0)≤3.2, DAS28(T3)≤3.2, and DAS28(T6)≤3.2), the same 16 (29%) patients showed stable RA.

The result of assessing about 39% of patients as having stable, low disease activity of RA might be regarded as remarkable in a disease like RA. Furthermore, as the intention is to include these patients in substitution based, shared care treatment, this finding becomes even more important as the number of patients with RA treated at a rheumatology outpatient department increases.

The interval of three months between measurements was derived from medical practice, in which patients usually do not see the doctor more often than four times a year. To establish the optimal number of consultations for patients with stable RA, and for the purpose of stability assessment, further research into the length of the interval between measurements should be started.

The loss of one third of the group of patients needs attention. The patients with missing data were older, reported a higher mean DAS28 score, and had a higher mean global disease activity. Conceivably, these patients had more often non-stable RA. If data had been available for these non-stable patients, the ICCs would have been smaller.

With respect to the ICC, it may well be that identical scores are obtained in successive administrations, thus resulting in a

**Table 4** Scores of patients on DAS28 at baseline (T0), differences between subsequent scores (T3-T0, T6-T0), and patients with stable, low disease activity of RA\*

	T0		T3-T0≤1.2		T3-T0≤0.6		T6-T0≤1.2		T6-T0≤0.6		Stable RA*	
	n	Cum%	n	Cum%	n	Cum%	n	Cum%	n	Cum%	n	Cum%
≥1.32 but <1.60	4	7.1	3	5.4	3	5.4	3	5.4	3	5.4	3	5.4
≥1.60 but <2.40	13	30.3	11	25.0	9	21.4	10	23.2	7	17.9	10	23.2
≥2.40 but <3.20	10	48.2	9	41.1	6	32.1	9	39.3	6	28.6	9	39.3
≥3.20 but <4.00	22	87.5	22	80.4	20	67.9	21	76.8	17	58.9	0	39.3
≥4.00 but <4.80	4	94.6	4	87.5	3	73.2	4	83.9	2	62.5	0	39.3
≥4.80 but <5.85	3	100.0	3	92.8	3	78.6	3	89.3	3	67.9	0	39.3

\*DAS28(T0)≤3.2 and DAS28(T6)-DAS28(T0)≤1.2.

high value for the ICC, but that the actual units checked differ greatly. Based on the ICCs of the response criteria, a group of patients with stable disease was identified.

In conclusion, this study shows the feasibility of assessing disease activity of outpatients with RA. Although developed to measure response we applied the DAS28 to assess stability—that is, low disease activity of RA in patients for the purpose of including patients in another study. A minority of outpatients could be classified as having stable, low disease activity of RA. This finding suggests that RA is a suitable chronic disease to which to apply a substitution based model of care delivery.

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