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ORIGINAL ARTICLE

Contribution of the Subjective Components of the Disease Activity Score to the Response to Biologic Treatment in Rheumatoid Arthritis

MAUD S. JURGENS,[1] CÉCILE L. OVERMAN,[2] JOHANNES W. G. JACOBS,[1] RINIE GEENEN,[3] BART V. J. CUPPEN,[1] ANNE C. A. MARIJNISSEN,[1] JOHANNES W. J. BIJLSMA,[1] PACO M. J. WELSING,[1] FLORIS P. J. G. LAFEBER,[1] AND JACOB M. VAN LAAR,[1] ON BEHALF OF THE UTRECHT ARTHRITIS COHORT STUDY GROUP

Objective. **A significant proportion of patients with rheumatoid arthritis do not respond adequately to biologic treatment. We hypothesized that lack of response to (biologic) disease-modifying antirheumatic drugs (DMARDs) is high in patients in whom the subjective, patient-reported component of the Disease Activity Score 28 (DAS28) is high at baseline. The primary aim of our present study was to investigate the contribution of the more subjective versus the objective components of the DAS28 to response to biologic agents in RA patients, as well as the changes in this contribution over time. The secondary aim was to examine whether the value of this subjective contribution at baseline affects the response to treatment.**

Methods. **The DAS28-P (the subjective components of the DAS28 relative to the total DAS28) was calculated. Patients were derived from the computer-assisted Management in Early Rheumatoid Arthritis Trial-II and the Biologicals and Outcome Compared and Predicted in Utrecht Region in Rheumatoid Arthritis Study. Ordinal logistic regression analyses were performed.**

Results. **The DAS28-P score at baseline was not associated with the level of response according to European League Against Rheumatism criteria at 3 months. Overall, a significant reduction in the DAS28-P score was observed 3 months after start of treatment, showing a greater reduction of the combined subjective components in good responders.**

Conclusion. **The results reject the hypothesis that the lack of response to biologic DMARDs is especially high in patients in whom the patient-reported component of the DAS28 is high at baseline; these subjective components are not linked to treatment response.**

INTRODUCTION

Treatment of rheumatoid arthritis (RA) has significantly improved through concepts such as "tight control" and "treat to target," as well as the introduction of biologic drugs. Currently, patients can not only use synthetic disease-modifying antirheumatic drugs (DMARDs), preferably in a treatment strategy with dose and medication adjustments tailored to the individual patient (1), but they can also use biologic DMARDs, increasing the chance of reaching remission (2,3). However, biologic DMARDs are not always effective (4). One reason could be that RA is probably the final common pathway for multiple, mutually related pathologic processes. It is therefore unlikely to be cured by a single treatment strategy. Individualized approaches are needed, propagated nowadays as an important next step in further improving treatment strategies for RA (3).

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[1]Maud S. Jurgens, PhD, Johannes W. G. Jacobs, MD, PhD, Bart V. J. Cuppen, MD, Anne C. A. Marijnissen, PhD, Johannes W. J. Bijlsma, MD, PhD, Paco M. J. Welsing, PhD, Floris P. J. G. Lafeber, PhD, Jacob M. van Laar, MD, PhD: University Medical Center Utrecht, Utrecht, The Netherlands; [2]Cécile L. Overman, MSc: Utrecht University, Utrecht, The Netherlands; [3]Rinie Geenen, PhD: University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands.

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Address correspondence to Maud S. Jurgens, PhD, Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, F02.127, PO Box 85500, 3508 GA Utrecht, The Netherlands. E-mail: mjurgens@umcutrecht.nl.

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Significance & Innovations

- The largest part of improvement in disease activity on average and especially in good responders can be accounted for by the subjective contribution to the Disease Activity Score in 28 joints (DAS28).
- Responders and nonresponders did not differ in the baseline subjective contribution, therefore the DAS28-P value at baseline could not be linked to treatment response.

Disease activity measures facilitate clinical decision-making (5). The most commonly used measure in RA to assess disease activity is the Disease Activity Score based on 28 joints (DAS28) (6). This composite clinical index is calculated by an algorithm of a value for 2 more subjective components, the tender joint count (TJC28) and the visual analog scale general well-being (VAS-GH) measure, and a value for 2 more objective components, the swollen joint count (SJC28) and the erythrocyte sedimentation rate (ESR). Although the DAS28 was only validated on a group level (6), this clinical score has been used widely to adjust the treatment of individual patients (7–9). When disease activity is measured through a (partly) symptom-based score like the DAS28, not all components may respond similarly to treatment. The more subjective components may be experienced differently by different patients, and this may vary over the disease course within a patient (10). The subjective components could also be influenced by comorbidities (fibromyalgia, stress, depression, outcome expectations, etc.). The high pain and disability scores seen in fibromyalgic RA suggest that these patients have high scores using summative assessments (11). If disease activity scores are disproportionately high in relation to the level of inflammatory synovitis in fibromyalgic RA, the value of disease activity assessments in these patients is questionable (11,12). Patients might still benefit from medication, but the effect on disease activity might be limited.

In clinical trials and daily practice, a significant proportion of RA patients does not respond satisfactorily to their biologic treatment. We hypothesized that RA patients with higher relative scores of TJC28 + VAS-GH have a higher probability of not responding to biologic treatment in comparison to the patients with more inflammatory disease activity as measured by SJC28 + ESR and therefore have a disproportionate contribution to the lack of response. Ideally, one would like to predict the response to biologic treatment before expectations and cost are being raised.

The primary aim of our present study was to investigate the contribution of the more subjective versus the objective components of the DAS28 to response to biologic agents in RA patients, as well as the changes in this contribution over time. The secondary aim was to find out if the value of this subjective contribution at baseline affects the response to treatment.

PATIENTS AND METHODS

CAMERA-II Trial and BiOCURA Study. Patients included in this study were selected from 2 databases of the Utrecht Arthritis Cohort Study Group (SRU), one resulting from the Computer Assisted Management in Early Rheumatoid Arthritis Trial-II (CAMERA-II) and one from the observational BiOCURA (Biologicals and Outcome Compared and Predicted in Utrecht Region in Rheumatoid Arthritis) study. These studies were approved by the ethical review boards of the participating hospitals. All patients had a diagnosis of RA according to the American College of Rheumatology criteria for RA (13) and gave written informed consent. Patients who started with their first biologic agent and who had DAS28 data available both at baseline (time of starting biologic treatment) and at the 3-month followup were included in this study (n = 172).

In the CAMERA-II trial, early RA patients were included between 2003 and 2008. Details of the CAMERA-II trial are reported elsewhere (14). In short, this trial compared the addition of 10 mg/day of prednisone or prednisone-placebo to a randomized, double-blind, prospective, multicenter 2-year methotrexate (MTX)–based tight-controlled treatment strategy, aiming for remission. All consecutive patients who visited the outpatient clinic of 1 of the 7 SRU rheumatology departments were asked to participate, and the included patients (n = 236) all gave written informed consent. This strategy included a final step of adding a biologic agent; that step was taken in 16 (of 117) patients receiving additional prednisone and 42 (of 119) patients receiving the additional prednisone-placebo. Out of these, 51 participants met the inclusion criteria of the present study. All 51 participants received adalimumab according to standard clinical practice guidelines.

In the ongoing observational BiOCURA cohort study, conducted by SRU centers, the first patient was enrolled in June 2009. This study aims to define (and in the future implement) recommendations and limitations for the use of each biologic agent on the market for treatment of RA, based on disease activity response to treatment via the clinical and immunologic profile of an individual patient. Every patient with RA who started a biologic agent could enter (and re-enter after a switch to another biologic agent) this study, before the first dose of the biologic agent. As of July 2013, 121 patients met the inclusion criteria of the present study (including starting with the first biologic agent) and were included in the present analysis. Of these 121 patients, the number of biologic DMARDs were mainly tumor necrosis factor (TNF) blockers and they were distributed as follows: 52 patients received adalimumab, 43 received etanercept, 10 received golimumab, 6 received infliximab, and 3 received certolizumab pegol; all doses were per Dutch standardized protocol. Seven patients did not receive a TNF blocker, i.e., 5 received tocilizumab (interleukin-6 blocker) and 2 received rituximab (destroys B cells) per protocol.

Statistical analysis. Descriptive statistics (mean with SD, median with interquartile range, and number with percentage) were used to quantitatively summarize the

Table 1. Baseline patient characteristics*

Characteristics	Total (n = 172)	BiOCURA (n = 121)	CAMERA-II (n = 51)	*P*
Age, years	52.0 ± 12.4	53.0 ± 11.9	50.5 ± 13.4	0.09
Female	128 (74)	93 (77)	35 (69)	0.26
RF-positive status	102 (67)†	71 (66)‡	31 (69)§	0.71
DAS28 start	4.11 ± 1.37	4.32 ± 1.18	3.61 ± 1.65	0.01
TJC28, median (IQR)	4.5 (2–11)	5 (2–11.5)	3 (0–9)	0.02¶
VAS-GH	46.78 (26.73)	54.01 (23.87)	29.55 (25.41)	< 0.001
SJC28, median (IQR)	2 (0–4)	2 (0–4)	2 (0–5)	0.11¶
ESR, median (IQR)	16.5 (7–30.75)	18 (9–31.5)	11 (5–30)	0.24¶
DAS28-P score#	0.44 ± 0.19	0.48 ± 0.18	0.34 ± 0.20	< 0.001
1st interquartile	43 (25)	21 (17)	22 (43)	< 0.001
2nd interquartile	43 (25)	31 (26)	12 (24)	0.85
3rd interquartile	43 (25)	32 (26)	11 (22)	0.57
4th interquartile	43 (25)	37 (31)	6 (12)	0.01
No. of prior synthetic DMARDs	2.48 ± 1.21	2.99 ± 1.05	1.27 ± 0.45	< 0.001
Smoking (%)	46 (26.7)**	28 (23.1)	18 (38.3)††	0.048

* Values are the number (%) for categorical variables and mean ± SD for continuous variables unless indicated otherwise. *P* value states whether there was a significant difference between the 2 subgroups. BiOCURA = Biologicals and Outcome Compared and Predicted in Utrecht Region in Rheumatoid Arthritis; CAMERA-II = Computer Assisted Management in Early Rheumatoid Arthritis Trial-II; RF = rheumatoid factor; DAS28 = Disease Activity Score in 28 joints; TJC = tender joint count; IQR = interquartile range; VAS-GM = visual analog scale general well-being measure; SJC = swollen joint count; ESR = erythrocyte sedimentation rate; DMARDs = disease-modifying antirheumatic drugs.
† N = 153 with reported RF status.
‡ N = 108 with reported RF status.
§ N = 45 with reported RF status.
¶ By Mann-Whitney U test.
# Fisher's exact test regarding the overall difference in interquartile distribution between the 2 subgroups: $P = 0.03$.
** N = 46 of 168 (4 patients with no reported data).
†† N = 18 of 47 (4 patients with no reported data).

distribution of the variables at baseline. Group differences between the 2 selections from the study populations, in means for continuous data, were tested for significance using independent *t*-tests or Mann–Whitney U test if not normally distributed. For differences in categorical data, chi-square tests were performed. Patient response to therapy was defined according the European League Against Rheumatism (EULAR) criteria for good, moderate, and nonresponders (15,16).

To quantify the size of the contribution of the subjective patient-reported domains of the DAS28 (TJC28 and VAS) relative to the total DAS28, a quantity (the DAS28-P) derived from the standard formula to calculate the DAS28 was calculated at baseline and at 3 months (10). The more subjective domain part of the DAS28 formula / total DAS28 formula =

$$\left(0.56\times\sqrt{\text{TJC28}}+0.014\times\text{VAS-GH}\right)/(0.56\times\sqrt{\text{TJC28}}+0.28\times\sqrt{\text{SJC28}}+0.70\times\ln[\text{ESR}]+0.014\times\text{VAS-GH})$$

The range for the VAS-GH is 0–100, and the range for ESR is approximately 0–140. Our null hypothesis stated that the DAS28-P score at the start is not significantly different between patients with different levels of response (i.e., good, moderate, nonresponse). Paired *t*-tests were performed to see if there was a significant difference (change) between the DAS28-P score at baseline and at 3 months within the patients with different levels of response; an analysis of variance was performed to test if this change was different between the different levels of response.

An ordinal logistic regression analysis was performed to investigate whether the DAS28-P score at baseline was associated with the different levels of response to treatment at 3 months, when the DAS28 score at the start and other possible predictors such as sex, age, and previous DMARD use were corrected for in the model.

Because the CAMERA-II subgroup was too small for multivariate analyses, the multivariable analyses for the second aim were performed on the total cohort only. Subgroups were used as covariate in the analyses.

All analyses were performed using SPSS software, version 20.0, and a *P* value of less than 0.05 was regarded as statistically significant.

RESULTS

The baseline characteristics of the total cohort and both subgroups are reported in Table 1. The DAS28 score, the subjective components of the DAS28 (TJC28 and VAS-GH), the DAS28-P score, the number of prior DMARDs, and the number of smokers were not equally distributed over the 2 cohorts, showing lower disease activity, a smaller DAS28-P score, and a lower number of prior synthetic DMARDs and smokers in the CAMERA-II trial (not surprisingly, this being an early RA cohort).

To address the primary aim, Table 2 shows the DAS28-P score for all patients, each subgroup, and per EULAR response group, both at baseline and after 3 months of treatment with a first biologic agent. The overall subjective contribution to the DAS28 was 44%, 48%, and

Table 2. The DAS28-P score and its change over time*

Cohort/EULAR response	No.	Baseline	3 months	*P*†
Total				
All	172	0.44 ± 0.19	0.35 ± 0.24	< 0.001
Good	65	0.46 ± 0.12	0.26 ± 0.24	< 0.001
Moderate	41	0.46 ± 0.12	0.42 ± 0.20	0.16
Non	66	0.40 ± 0.26	0.39 ± 0.23	0.66
BiOCURA				
All	121	0.48 ± 0.18	0.38 ± 0.24	< 0.001
Good	50	0.47 ± 0.12	0.28 ± 0.25	< 0.001
Moderate	29	0.47 ± 0.17	0.44 ± 0.21	0.40
Non	42	0.49 ± 0.24	0.47 ± 0.20	0.36
CAMERA-II‡				
All	51	0.34 ± 0.20	0.27 ± 0.21	0.004
Good	15	0.42 ± 0.11	0.19 ± 0.13	< 0.001
Moderate	12	0.44 ± 0.18	0.39 ± 0.19	0.09
Non	24	0.24 ± 0.21	0.26 ± 0.23	0.57

* DAS28-P = Disease Activity Score in 28 joints, subjective components; EULAR = European League Against Rheumatism; BiOCURA = Biologicals and Outcome Compared and Predicted in Utrecht Region in Rheumatoid Arthritis; CAMERA-II = Computer Assisted Management in Early Rheumatoid Arthritis Trial-II.
† The reported *P* value represents the level of significance of the performed paired *t*-tests.
‡ Start contribution score not equally distributed in CAMERA-II; $P = 0.003$ by analysis of variance.

34%, respectively, at the start in the total cohort and the separate BiOCURA and CAMERA-II subgroups. At the start, the DAS28-P score did not differ between the response groups in the total and BiOCURA subgroups (all between 40% and 49%). Only the nonresponders in the CAMERA-II sample had a lower subjective contribution and differed significantly from the other response groups in that subgroup; DAS28-P scores were 0.42, 0.44, and 0.24 for the good, moderate and nonresponders, respectively ($F = 6.65$, $P = 0.003$). Overall, a significant change in the DAS28-P score was observed over time in both the total ($P < 0.001$) and the separate BiOCURA cohort and CAMERA-II subgroups ($P < 0.001$ and $P = 0.004$, respectively), showing a smaller subjective contribution. This can be interpreted as more pronounced improvement in the subjective parts of the DAS28. Interestingly, this significant reduction of the DAS28-P score was only observed in the good responders ($P < 0.001$) in the total cohort as well as the subgroups.

Regarding the second aim, Table 3 shows that the DAS28-P score at baseline was not associated with the different levels of response to treatment at 3 months. The model did show that lower age, a higher baseline DAS28 score, a lower number of prior synthetic DMARDs used, being in the BiOCURA cohort subgroup, and being male resulted in an increase in odds of being in a higher level of response. When the regression analysis was performed without the variable DAS28 at baseline, the DAS28-P score was not significantly associated with the level of response.

DISCUSSION

The primary aim of our present study was to investigate the presumed disproportionate contribution of the subjective components of the DAS28 score in the disease activity score in patients who do not respond well to treatment and to see if the subjective contribution changes over time after the start of a new treatment step in a cohort of RA patients treated with biologic agents.

We hypothesized that objective, doctor-observed and laboratory measures would have a higher contribution at baseline (i.e., before the start of biologic treatment) in responders and that these parameters would improve more significantly after the start of this treatment.

Our findings do not support this, as the subjective components (TJCs) and 1 of the objective components (ESR) of the DAS28 contributed most to the clinical response.

We conclude, therefore, that a disproportionate subjective contribution to the DAS28 score is not the reason for nonresponse. However, the share of the subjective components of the DAS28 became smaller over time in patients with a good response to the therapy, suggesting that in good responders especially also the subjective components improve, whereas none of the items of the DAS28 seem to respond in the nonresponder group. The EULAR response groups in the cohort and subgroups did not differ much. In general (the one exception being the nonresponders in the CAMERA-II subgroup), the DAS28-P score became smaller over time. The results suggest that biologic DMARDs affect, through their blocking ability on proinflammatory cytokines, both inflammation (disease) and subjective components of the diseases (illness

Table 3. Ordinal regression analysis predicting level of response to treatment at 3 months from multiple variables*

Variables	*p*OR†	Estimate	*P*
DAS28-P score at baseline ×100‡	1.00	0.00	0.88
DAS28 at baseline	1.68	0.52	< 0.001
Age, years	0.97	−0.04	0.02
No. of prior DMARDs	0.63	−0.46	0.02
Subgroups			
CAMERA-II	0.34	−1.008	0.04
BiOCURA			
Female sex	0.39	−0.94	0.03
RF positive	1.32	0.28	0.43
Smoker (yes)	0.69	−0.37	0.33

* Ordinal logistic regression with variables obtainable at baseline. This analysis is performed to address the odds of being in a higher European League Against Rheumatism response group. Good response is the reference category. Model information: logit; −2 log likelihood final vs. intercept: $P < 0.001$; Nagelkerke's $R^2 = 0.19$; test of parallel lines: $P = 0.21$. OR = odds ratio; DAS28-P = Disease Activity Score in 28 joints, subjective components; DMARDs = disease-modifying antirheumatic drugs; CAMERA-II = Computer Assisted Management in Early Rheumatoid Arthritis Trial-II; BiOCURA = Biologicals and Outcome Compared and Predicted in Utrecht Region in Rheumatoid Arthritis; RF = rheumatoid factor.
† Proportional OR.
‡ Contribution score ranges between 0 and 1 because it is a ratio; for clear interpretation of the particular estimate, this ratio has been multiplied by 100. When the regression analysis was performed without the variable DAS28 at baseline, the DAS28-P score was not significantly associated with the level of response; n = 151 due to missing data.

or sickness response) (17–19). In patients with RA, the swift effect of a blockade of TNF has been described, showing a significant lowering in the subjective VAS-pain within 24 hours (20). These data indicate a fast effect of TNF blockade on the pain responses in the central nervous system even before a measurable antiinflammatory effect is achieved (20).

Regarding our secondary aim, we found that the DAS28-P score at baseline is not associated with the different levels of response to treatment at 3 months. These results make it difficult to base treatment decisions on the subjective or objective characteristics of disease activity scores.

Recently, a new criterion for treatment response as assessed by the DAS28 that exceeds random disease activity variations in patients with RA has been established, which may be useful in steering individual therapy and stratifying clinical trials (21).

The present study has some limitations. The baseline characteristics were not all equal between the 2 subgroups. This can be explained by the difference in study design. CAMERA-II is a highly protocolized strategy trial using an MTX-based treatment strategy, with stringent steps to follow and only included early RA patients. The BiOCURA cohort is an observational study where patients with varying disease durations are enrolled. Patients in the CAMERA-II trial might be making the step to a biologic agent more quickly, as the next protocolized step following MTX (plus prednisone or a placebo), than in the BiOCURA cohort, where response is more based on current disease status, inflammation, patient perception, clinical observations, and other treatment options (such as when other synthetic DMARDs are not [no longer] an option). Another limitation of our study is that we do not possess information on fibromyalgia, stress, depression, and outcome expectations, which could have influenced our outcomes. New study designs should include this type of patient information.

The DAS28-P score has not been widely used. While some studies have used the subjective contribution of the DAS28 to study DMARD intensification (22), its role in predicting pain (10), and how this contribution is affected by psychological factors (23), to our knowledge no studies have focused on the association between the subjective contribution and response to treatment. There might be some issues calculating the DAS28-P under extreme value conditions. For high values of the DAS28 (therefore all contributors of the DAS28 are high), the DAS28-P score is forced toward a value of approximately 0.5. In contrast, if the DAS28-P is either way close to 0 or close to 1, then only moderate scores of the DAS28 (± 4) are possible. In our study, these extreme value conditions were absent.

The counterintuitive findings of an equal contribution of the subjective disease activity measures irrespective of response and the even larger improvement in subjective measures of the DAS28 in good responders might (partly) be a placebo effect, possibly related to the use of biologic DMARDs. It is also not clear if over time this effect is the same.

For clinical practice we can conclude that pain at baseline is not a reason to not start with biologic DMARDs and that the presented data do not support patient selection based on subjective contribution to disease activity.

More research is needed for better understanding and more insight into the precise working of biologic DMARDs on more subjective patient-reported outcomes, so biologic DMARDs can be used for treating the individual patient optimally. It would be of great interest to learn if in placebo-controlled biologic DMARD research similar effects of equal contribution of subjective and objective measures to disease activity irrespective of response are found in RA patients.

Our study shows that the largest part of improvement in disease activity on average and especially in good responders can be accounted for by the subjective contribution to the DAS28. The hypothesis that especially the subjective, patient-reported components of the DAS28 have a disproportionate contribution to the lack of response to biologic DMARD treatment was rejected. Responders and nonresponders did not differ in the baseline subjective contribution; therefore the DAS28-P score at baseline could not be linked to treatment response.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Jurgens had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Jurgens, Overman, Jacobs, Geenen, Bijlsma, Welsing, Lafeber, van Laar.

Acquisition of data. Jurgens, Cuppen, Marijnissen.

Analysis and interpretation of data. Jurgens, Overman, Jacobs, Geenen, Welsing, Lafeber, van Laar.

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