A Multibiomarker Disease Activity Score for Rheumatoid Arthritis Predicts Radiographic Joint Damage in the BeSt Study

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ABSTRACT. ***Objective.*** To determine whether a multibiomarker disease activity (MBDA) score predicts radiographic damage progression in the subsequent year in patients with early rheumatoid arthritis.

Methods. There were 180 serum samples available in the BeSt study (trial numbers NTR262, NTR 265): 91 at baseline (84 with radiographs available) and 89 at 1-year followup (81 with radiographs available). Radiographs were assessed using the Sharp/van der Heijde Score (SvdH). Twelve serum biomarkers were measured to determine MBDA scores using a validated algorithm. Receiver-operating curves and Poisson regression analyses were performed, with Disease Activity Score (DAS) and MBDA score as independent variables, and radiographic progression as dependent variable.

Results. At baseline, MBDA scores discriminated more between patients who developed radiographic progression (increase in SvdH ≥ 5 points) and patients who did not [area under the curve (AUC) 0.767, 95% CI 0.639–0.896] than did DAS (AUC 0.521, 95% CI 0.358–0.684). At 1 year, MBDA score had an AUC of 0.691 (95% CI 0.453–0.929) and DAS had an AUC of 0.649 (95% CI 0.417–0.880). Adjusted for anticitrullinated protein antibody status and DAS, higher MBDA scores were associated with an increased risk for SvdH progression [relative risk (RR) 1.039, 95% CI 1.018–1.059 for baseline MBDA score; 1.037, 95% CI 1.009–1.065 for Year 1 MBDA score]. Categorized high MBDA scores were also correlated with SvdH progression (RR for high MBDA score at baseline 3.7; low or moderate MBDA score as reference). At 1 year, high MBDA score gave a RR of 4.6 compared to low MBDA score.

Conclusion. MBDA scores predict radiographic damage progression at baseline and during disease course. (J Rheumatol First Release Aug 15 2014; doi:10.3899/jrheum.131412)

Key Indexing Terms:
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Extensive progress in the treatment of rheumatoid arthritis (RA) has been made during the last decades. Prevention or minimization of radiographic joint damage progression is now a realistic treatment goal. Identifying patients at greatest risk of joint damage progression is a key challenge in the management of RA, allowing the optimal treatment for an individual patient.

Various models have been developed to predict (rapid) radiological progression in patients with RA[1,2,3]. These models have identified clinical features such as swollen joint count and C-reactive protein (CRP), presence of autoantibodies rheumatoid factor and anticitrullinated protein antibodies (ACPA), bone erosions at baseline, and initial treatment as predictors. These models provide an estimation of the risk to develop joint damage progression. However, exact risk estimation and risk estimation during disease course is still in the future.

Recently, a multibiomarker disease activity (MBDA)

score was developed[4], derived from 12 different serum proteins. This MBDA score shows a high correlation with conventional 28-joint Disease Activity Score (DAS28)[5]. Because the indices of the disease activity score have an association with radiographic joint damage, MBDA score might also be a promising candidate for predicting radiographic damage progression[6].

Our study aimed to investigate the predictive value of MBDA score at baseline, i.e., in disease-modifying antirheumatic drug (DMARD)-naive patients with early RA, and after 1 year of targeted treatment aiming at low disease activity, based on the 44-joint Disease Activity Score (DAS), with radiographic joint damage progression in the subsequent year as the main outcome.

MATERIALS AND METHODS

Dataset. Data for this posthoc analysis were obtained from the BeSt (Dutch acronym for treatment strategies) study (trial registration numbers NTR262 and NTR265)[7]. In this multicenter randomized trial of 508 patients with early RA who fulfilled the 1987 American College of Rheumatology revised criteria for diagnosis of RA[8], patients were allocated to 1 of 4 treatment strategies and received (1) sequential monotherapy, (2) step-up combination therapy, (3) initial combination therapy with prednisone, or (4) initial combination therapy with infliximab. Clinical assessments were performed every 3 months. All strategies were based on the treat-to-target principle, with treatment adjustments as long as 44-joint DAS was > 2.4. Radiographs of hands and feet were performed at baseline and then yearly. Radiographs were scored in random order using the Sharp van der Heijde Score (SvdH) by 2 independent readers, blinded to patient identity.

For this analysis, 180 serum samples were available from 125 patients, with 91 samples from baseline and 89 samples from 1-year followup. For 55 patients, samples of both timepoints were available. Of the other patients in the BeSt study, insufficient or no serum samples were stored.

Serum biomarker measurement. Serum samples were stored at –80°C. Twelve biomarkers were measured: epidermal growth factor (EGF), vascular endothelial growth factor A (VEGF-A), leptin, interleukin 6 (IL-6), serum amyloid A, CRP, vascular cell adhesion molecule 1 (VCAM-1), matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 3 (MMP-3), tumor necrosis factor receptor superfamily member 1A (TNF-RI), human cartilage glycoprotein 39 (YKL-40), and resistin[4]. The biomarkers were measured with immunoassays using 3 custom multiplex panels on the Meso Scale Discovery Sector Imager 6000: panels A (for EGF, IL-6, leptin, and VEGF-A), B (for CRP, SSA, and VCAM-1), and C (for MMP-1, MMP-3, resistin, TNF-RI, and YKL-40). Concentrations were calculated using standard curves with 4 parameter logistic regression curve fits[4].

MBDA algorithm. The MBDA algorithm (Vectra DA algorithm score) has been validated and described previously[4,9,10]. The MBDA score is calculated by an algorithm in which levels of 12 biomarkers, mentioned in the previous paragraph, are entered. The MBDA score is calculated from the serum concentrations of 12 biomarkers by a validated algorithm and ranges from 1 to 100. Established thresholds for the MBDA score are low disease activity (< 30), moderate disease activity (30–44), and high disease activity (> 44)[9]. DAS was categorized as follows: remission (DAS < 1.6)[11], low disease activity (DAS ≥ 1.6–2.4), moderate disease activity (DAS > 2.4–3.7), and high disease activity (DAS > 3.7). DAS remission and low DAS were combined to form 1 category, indicated as low DAS.

Statistics. Baseline characteristics for the 125 patients in the BeSt study with serum samples for MBDA analysis were compared to the 383 patients without serum samples. The baseline characteristics between the 2 groups were compared using Wilcoxon's rank-sum test or chi-square test as appropriate.

Patients with MBDA score at baseline (n = 91) and patients with MBDA score at 1-year followup (n = 89) were analyzed as separate groups, to allow for the effect of DAS-steered treatment adjustments during the first year of treatment. Patients with samples available at both timepoints were analyzed per sample in both groups. All analyses described below were performed for both groups separately.

The predictive value of the MBDA score was compared to the predictive value of the DAS. Patients were cross-categorized by baseline DAS and baseline MBDA score to evaluate agreement and discordance between these measures. Patients with DAS and MBDA score at Year 1 were cross-categorized in the same manner. Radiographic progression, using pairs of radiographs (baseline and 1 yr, or Yr 1 and Yr 2) defined by an increase in SvdH in the year after biomarker measurement, was the main outcome in our study. The change in SvdH at each timepoint is summarized according to disease activity category as defined by DAS and MBDA score.

Receiver-operating curves characteristic (ROC) were used to determine whether MBDA scores can discriminate between the occurrence and nonoccurrence of radiographic progression. For this analysis, 2 different cutoffs were used and analyzed separately. Patients with increases in SvdH of ≥ 0.5 and ≥ 5 points were considered to have radiographic progression. The latter threshold is similar to the smallest detectable difference in the first year of the BeSt study[7] and the first was chosen to differentiate 2 equal-sized groups in which any progression could be compared to no progression at all. ROC were used to calculate the area under the curve (AUC), with DAS or MBDA score as the independent variable and the occurrence of radiographic progression as the dependent variable based on each threshold. The AUC for MBDA scores were then compared to the AUC for DAS.

Univariate Poisson regression analysis was performed based on the change in SvdH from baseline to Year 1 as the dependent variable, and baseline DAS, MBDA, and ACPA status as the independent variables. Then, the independent variables were combined in a multivariate Poisson regression analysis. One has to take into consideration that the units indicating change in DAS, MBDA score, and ACPA are different when interpreting the relative risks (RR). One unit in ACPA indicates the difference between positivity and negativity, while each 1 unit increase in MBDA score (on a scale from 1 to 100) represents successively higher levels of disease activity.

For the univariate analysis, the MBDA score was evaluated without categorization and with categorization (low/moderate vs high). Similar models were used to evaluate the change in SvdH from Year 1 to Year 2.

RESULTS

Patient characteristics. Most baseline characteristics of the 125 patients with serum samples were similar to those of patients in the BeSt study who lacked serum samples and were not included in our study (n = 383; Appendix 1). Patients with serum samples available were equally distributed among the treatment arms (p = 0.220). However, among the patients with samples available for testing of biomarkers, there were statistically significantly more females (75% vs 65%), and tender joint counts were lower [median (interquartile range; IQR) 11 (7–16) vs 14 (10–19)]. In addition, patients with samples available for biomarkers had fewer erosions [median (IQR) 1.0 (0.5–3.0)] than did patients without samples available [median (IQR) 2.0 (0.5–5.5)].

When patients were cross-categorized by MBDA score and 44-joint DAS, concordance of categories was observed for 56 of 91 patients (62%) at baseline and 35 of 89 patients (39%) at 1 year (Table 1). At 1 year, DAS categories indicate

Table 1. Patients categorized by MBDA score and DAS at baseline (A), and at 1 year (B). Values indicate the number of patients per category.

A.	DAS at Baseline			
	Low (≤ 2.4)	Moderate (> 2.4–3.7)	High (> 3.7)	Total
MBDA at baseline				
Low (30)	1	0	6	7
Moderate (30–44)	0	3	7	10
High (> 44)	0	22	52	74
Total	1	25	65	91
B.	DAS at 1 Year			
MBDA at 1 yr				
Low (< 30)	26	7	0	33
Moderate (30–44)	24	6	2	32
High (> 44)	13	8	3	24
Total	63	21	5	89

DAS: Disease Activity Score; MBDA: multibiomarker disease activity score.

more patients in low disease activity, while MBDA scores in this category are also in moderate and high category.

Cross-categorizing MBDA score and treatment strategy, differences in MBDA scores between the randomization arms were not observed at baseline, or at 1 year (data not shown).

Presence of radiological progression. Baseline and 1-year radiographs were available for 84 of the 91 patients with MBDA scores at baseline. Median (IQR) change ( ) in SvdH from baseline to 1 year was 0.0 (0.0–2.5), with 49 patients (58%) showing no radiographic progression (SvdH ≤ 0).

Radiographs at 1 year and 2 years were available for 81 of the 89 patients with MBDA scores at 1 year. The median (IQR) SvdH was 0.0 (0.0–1.3), with 51 patients (63%) showing no radiographic progression during this year.

In Figure 1, SvdH progression per DAS and MBDA category is shown. From baseline to Year 1, most patients shift from high to low DAS. MBDA scores are also lower at 1 year, but more patients are in the moderate or high category.

Predictive value of the MBDA score. At baseline, the MBDA score appeared to discriminate more between no radiographic progression and radiographic progression ≥ 0.5 point in the subsequent year (AUC 0.606, 95% CI 0.482–0.729) than the DAS (AUC 0.373, 95% CI 0.248–0.498). The same was true for SvdH ≥ 5 points (AUC for MBDA score 0.767, 95% CI 0.639–0.896; AUC for DAS 0.521, 95% CI 0.358–0.684).

The MBDA score at 1 year differentiated more between no damage progression and progression ≥ 0.5 point during the second year (AUC 0.686, 95% CI 0.564–0.809) than could the DAS (AUC 0.527, 95% CI 0.392–0.663). This was also true for the discrimination of SvdH ≥ 5 points as outcome for MBDA score (AUC 0.691, 95% CI 0.453–0.929) compared with DAS at 1 year (AUC 0.649, 95% CI 0.417–0.880).

Higher MBDA scores at baseline were associated with SvdH progression in the subsequent year (Table 2). This correlation was also found for ACPA. At 1 year, MBDA score, DAS, and ACPA were all associated with SvdH progression in the second year.

Higher MBDA scores measured at baseline were also independently associated with an increased risk for SvdH progression in the subsequent year, adjusted for ACPA positivity and DAS (RR 1.039, 95% CI 1.018–1.059; Table 3). For each 10-unit increase in baseline MBDA score, there was a 1.47-fold increase in the risk of progression at Year 1.

For patients with MBDA scores at 1-year followup, a similar effect was found (RR 1.037, 95% CI 1.009–1.065), indicating a 1.44-fold higher risk of progression at Year 2 for each 10-unit increase in the MBDA score at Year 1.

A high category of baseline MBDA score was associated with a significantly greater risk of SvdH progression in the subsequent year than a moderate or low MBDA score (RR 3.738, 95% CI 1.448–9.655). The same was true for a high category of MBDA score at 1 year (RR 4.621, 95% CI 1.339–15.949) compared to a low MBDA score. However, moderate MBDA scores at 1 year were not associated with a significantly higher risk than low MBDA scores for SvdH progression in the subsequent year (RR 1.437, 95% CI 0.454–4.545).

DISCUSSION

Our study aimed to determine the ability of MBDA scores to predict radiographic joint damage progression in DMARD-naive patients with early RA being treated with treat-to-target strategies. Predicting which patients will develop radiographic damage progression remains one of the major challenges in the management of RA, and may help physicians to make treatment decisions.

The main finding of our study was that MBDA score was indeed an independent predictor for radiological damage progression defined as an increase of SvdH score in the subsequent year[11a]. MBDA scores resulted in ROC with greater AUC values for SvdH progression than DAS, both at baseline and after 1 year of treatment, and for both definitions of radiological damage progression. In addition, we demonstrated that higher MBDA scores were associated with an increased risk for radiological damage progression, with RR = 1.039 for MBDA score at baseline and RR = 1.032 after 1 year (adjusted for ACPA and DAS). Categorized MBDA scores showed the same trend. ACPA showed an even higher RR. However, ACPA does not fluctuate very much over time and therefore does not represent current disease activity.

Previous studies have shown MBDA scores correlate with DAS28[5,9,12], which counts 28 joints and has been associated with radiographic progression. In our current

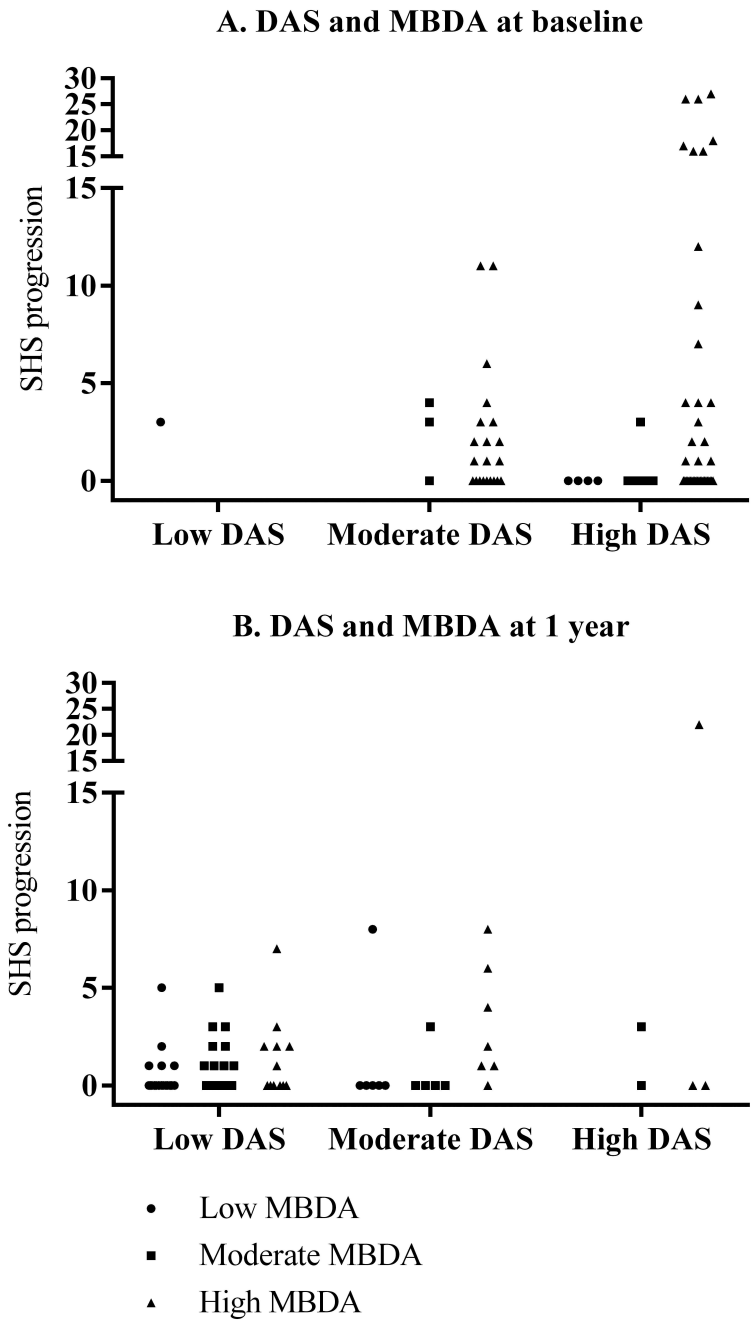

Figure 1. Change in Sharp/van der Heijde score (SHS; 0–448 scale); from baseline to 1 year (A) and from 1 year to 2 years (B) for patients stratified by DAS and MBDA score at baseline (A) or at 1 year (B). DAS: Disease Activity Score; MBDA: multibiomarker disease activity.

study, we looked at the DAS, which includes a 44-joint count for joint swelling and a 53-joint count for joint tenderness. For a majority of patients, the category of DAS and MBDA score were in agreement at baseline, when patients generally had active disease before the start of treatment. Still, in some patients at baseline and about half at 1 year, the category of MBDA score was higher than for DAS (Table 1). This result suggests that if DAS is low, the MBDA score might show residual disease activity that may be linked to SvdH progression in the subsequent year. This might reflect the inclusion of inflammatory markers such as IL-6, and molecules relevant to bone and cartilage damage, such as YKL-40, MMP-1, and MMP-3, in the MBDA test. In a previous study, patients in DAS28-CRP remission were

Table 2. Results of univariate Poisson regression analysis with MBDA (continuous), DAS, or ACPA as independent variables, and SvdH progression as dependent variable.

Baseline, n = 84	Risk for SvdH Progression Baseline – Year 1 RR	95% CI
DAS	1.068	0.775–1.472
MBDA	1.038	1.017–1.060
ACPA positivity	3.482	1.172–10.341
At 1 yr, n = 81	**Risk for SvdH Progression Year 1–Year 2 RR**	**95% CI**
DAS	2.040	1.127–3.690
MBDA	1.056	1.024–1.088
ACPA positivity	2.836	1.156–6.958

MBDA: multibiomarker disease activity; DAS: Disease Activity Score; ACPA: anticitrullinated protein antibodies; SvdH: Sharp van der Heijde score; RR: relative risk.

Table 3. Results of multivariate Poisson regression analysis with MBDA (continuous), DAS, and ACPA as independent variables, and SvdH progression as dependent variable.

Baseline, n = 84	Risk for SvdH Progression Baseline – Yr 1 RR	95% CI
DAS	0.952	0.673–1.346
MBDA	1.039	1.018–1.059
ACPA positivity	3.227	1.045– 9.970
At 1 yr, n = 81	**Risk for SvdH Progression Yr 1–Yr 2 RR**	**95% CI**
DAS	1.450	0.969– 2.169
MBDA	1.037	1.009– 1.065
ACPA positivity	2.339	1.027–5.325

MBDA: multibiomarker disease activity; DAS: Disease Activity Score; ACPA: anticitrullinated protein antibodies; SvdH: Sharp van der Heijde score; RR: relative risk.

found to be at greater risk for progression of radiographic joint damage if they had a high MBDA score, and MBDA-defined remission was found to be a predictor for suppression of progressive joint damage[13]. The association of the MBDA score at Year 1 with radiological damage progression 1 year later is less strong, probably because after initiation of (DAS-steered) treatment, disease activity and damage progression are quite well suppressed.

A limitation of our study is that the treat-to-target strategy suppressed inflammation and progression of radiographic joint damage in the majority of patients during the first year. In this early stage of the disease, damage progression rates will have no immediate clinical significance, although they may predict future disability from accumulated, irreversible damage[14]. MBDA scores appear to be sufficiently sensitive to underlying mechanisms of joint damage to predict even these low progression rates. Poisson regression analyses with radiographic progression as a continuous outcome supported this. Another limitation of our study is that MBDA scores were only available at baseline and at 1-year followup. The latter may represent patients with RA in a slightly more stable phase of their disease, but to see whether MBDA scores in established disease also predict future radiographic progression, sampling in a cohort including patients with RA of longer disease duration might be of additional value.

For patients with recent-onset RA who received treat-to-target therapy, MBDA scores at baseline and at 1 year predicted radiographic damage progression in the subsequent year. Further research is needed to establish the role of the MBDA score in clinical practice in predicting future joint damage and potentially steering treatment choices; to understand how it performs in patients with different stages of the disease; and to compare it to other predictors of damage progression such as CRP and ESR, and composite scores that include physical examination such as Simplified Disease Activity Index and Clinical Disease Activity Index; and magnetic resonance imaging and other imaging techniques.

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REFERENCES

1. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ronday HK, Seys PE, Kerstens PJ, et al. A matrix risk model for the

prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis 2010;69;1333–7.
2. Fautrel B, Granger B, Combe B, Saraux A, Guillemin F, Le Loet X. Matrix to predict rapid radiographic progression of early rheumatoid arthritis patients from the community treated with methotrexate or leflunomide: results from the ESPOIR cohort. Arthritis Res Ther 2012;14:R249.
3. Vastesaeger N, Xu S, Aletaha D, St Clair EW, Smolen JS. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. Rheumatology 2009;48:1114–21.
4. Centola M, Cavet G, Shen Y, Ramanujan S, Knowlton N, Swan KA, et al. Development of a multi-biomarker disease activity test for rheumatoid arthritis. PloS One 2013;8:e60635.
5. Hirata S, Dirven L, Shen Y, Centola M, Cavet G, Lems WF, et al. A multi-biomarker score measures rheumatoid arthritis disease activity in the BeSt study. Rheumatology 2013;52:1202–7.
6. Klarenbeek NB, Koevoets R, van der Heijde DM, Gerards AH, Ten Wolde S, Kerstens PJ, et al. Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis. Ann Rheum Dis 2011;70:1815–21.
7. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381–90.
8. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
9. Curtis JR, van der Helm-van Mil AH, Knevel R, Huizinga TW, Haney DJ, Shen Y, et al. Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. Arthritis Care Res 2012;64:1794–803.
10. Eastman PS, Manning WC, Qureshi F, Haney D, Cavet G, Alexander C, et al. Characterization of a multiplex, 12-biomarker test for rheumatoid arthritis. J Pharm Biomed Anal 2012;70:415–24.
11. Prevoo ML, van Gestel AM, van T Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996;35:1101–5.
11a. Hambardzumyan K, Bolce R, Saevarsdottir S, Cruickshank SE, Sasso EH, Chernoff D, et al. Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Ann Rheum Dis 2014 May 8 (E-pub ahead of print).
12. Bakker MF, Cavet G, Jacobs JW, Bijlsma JW, Haney DJ, Shen Y, et al. Performance of a multi-biomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. Ann Rheum Dis 2012;71:1692–7.
13. van der Helm-van AH, Knevel R, Cavet G, Huizinga TW, Haney DJ. An evaluation of molecular and clinical remission in rheumatoid arthritis by assessing radiographic progression. Rheumatology 2013;52:839–46.
14. Smolen JS, Aletaha D, Grisar JC, Stamm TA, Sharp JT. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. Ann Rheum Dis 2010;69:1058–64.

APPENDIX 1. Baseline characteristics.

Characteristics	Biomarkers, n = 125	No Biomarkers, n = 383	p
Sex, n (%) female	94 (75.2)	249 (65.0)	0.037
Age, mean (SD)	53 (14)	55 (14)	0.156
Treatment strategy, n (%)			0.220
Monotherapy	23 (18.4)	103 (26.9)	
Step-up therapy	29 (23.2)	92 (24.0)	
Initial combination with prednisone	38 (30.4)	95 (24.8)	
Initial combination with infliximab	35 (28.0)	93 (24.3)	
Rheumatoid factor positive, n (%)	78 (62.4)	251 (65.5)	0.524
ACPA-positive, n (%)	70 (56.0)	221 (57.8)	0.177
DAS44, mean (SD)	4.30 (0.87)	4.46 (0.86)	0.069
DAS28, mean (SD)	5.82 (1.03)	5.98 (1.00)	0.126
VAS general health (mm), mean (SD)	53.4 (22.0)	52.0 (19.5)	0.492
Tender joint count, median (IQR)	11.0 (7–15.5)	14.0 (10–19)	< 0.001
Swollen joint count, median (IQR)	13.0 (10–19)	14.0 (10–18)	0.957
ESR (mm/h), median (IQR)	36 (19–57)	37 (20–51)	0.971
C-reactive protein, median (IQR)	21 (9–59)	21 (8–49)	0.459
HAQ, mean (SD)	1.4 (0.7)	1.4 (0.7)	0.651
Erosions, median (IQR)	1.0 (0.5–3.0)	2.0 (0.5–5.5)	0.005
BMI, mean (SD)	26.0 (4.2)	26.0 (4.2)	0.860

ACPA: anticitrullinated protein antibodies; DAS44: Disease Activity Score at 44-joint count; DAS28: Disease Activity Score at 28-joint count; VAS: visual analog scale (range 0–100 mm); IQR: interquartile range; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire (range 0–3); BMI: body mass index.