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Predictive Ability, Validity, and Responsiveness of the Multi-Biomarker Disease Activity Score in Patients with Rheumatoid Arthritis Initiating Methotrexate

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Abstract

Background/Objective: We assessed the predictive value, validity, and responsiveness of the multi-biomarker disease activity (MBDA) score in rheumatoid arthritis (RA) patients initiating methotrexate.

Methods: We examined data from a 16-week, open-label study of methotrexate in RA. Disease activity was assessed and the MBDA score was calculated using serum that was collected and banked from baseline and week 16. Multivariable logistic regression models assessed whether MBDA scores predicted treatment response. Pearson correlations assessed the convergent validity and external responsiveness of the MBDA score with other measures of RA disease activity. Internal responsiveness was assessed by calculating standardized response means (SRMs).

Results: A total of 130 patients initiated the study, with follow-up MBDA scores available on 95 patients. Baseline MBDA scores did not predict ACR response or achieving low disease activity. Higher baseline DAS28-ESR scores were significantly associated with an ACR20 response (odds ratio 1.89 per unit, 95% CI 1.20–2.96) but not ACR50, ACR70, or low disease activity. The MBDA score moderate-to-weakly correlated with the DAS28-ESR and ESR at baseline and week 16, with weak-to-very weak correlations with patient global and function. Change in MBDA scores moderately correlated with changes in DAS28-ESR and ESR, while weakly correlating with changes in patient global and function. The DAS28-ESR (SRM 1.31) demonstrated greater responsiveness following methotrexate treatment than the MBDA score (SRM 0.71).

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Conclusions: MBDA scores did not predict treatment response to methotrexate. The MBDA score weak-to-moderately correlated with baseline and post-treatment disease activity measures and was less responsive to methotrexate-related improvement than the DAS28-ESR.

Keywords

Rheumatoid arthritis; MBDA score; Biomarker; Disease activity; Responsiveness; Psychometrics

Introduction

There are several tools available to measure disease activity in patients with rheumatoid arthritis (RA). The American College of Rheumatology (ACR) recommends the use of the Clinical Disease Activity Index (CDAI), Disease Activity Score with 28-joint counts with erythrocyte sedimentation rate (DAS28-ESR) or C-reactive protein (DAS28-CRP), Patient Activity Scale-II (PAS-II), Routine Assessment of Patient Index Data with 3 measures (RAPID-3), and Simplified Disease Activity Index (SDAI), as these are clinically feasible to perform at the point-of-care, accurate, sensitive to change, and able to discriminate between disease activity states [1]. Because factors besides RA disease activity such as comorbid conditions (e.g. fibromyalgia, osteoarthritis) may affect these scores, there is ongoing interest in discovering and testing novel RA disease activity measures.

The multi-biomarker disease activity (MBDA) score is a laboratory test incorporating the measurement of twelve biomarkers to calculate a disease activity score ranging from 1 to 100 [2]. A recent systematic review demonstrated the convergent validity of the MBDA score with several established RA disease activity measures, finding weak-to-moderate correlations in scores ($r = 0.23$ to 0.48) [3]. However, treatment with disease-modifying anti-rheumatic drugs (DMARDs), such as tocilizumab, may influence the validity of the MBDA score for assessing RA disease activity. In a study by Reiss et al. [4], correlation between the MBDA score and DAS28-CRP was found to be lower following 24 weeks of tocilizumab therapy than at baseline. Treatment with tocilizumab, a monoclonal antibody that functions as an antagonist of the interleukin-6 (IL-6) receptor, was shown to decrease CRP levels (a component of both the DAS28-CRP and MBDA score) while increasing IL-6 levels (a component of the MBDA score). It was postulated that the substantial increases seen in IL-6 levels led to a decreased ability of the MBDA score to assess clinical response to tocilizumab. An additional study by Fleischmann et al. [5] suggested that the MBDA score may not correlate with established disease activity measures after treatment with adalimumab or abatacept. Furthermore, patients in this study treated with abatacept exhibited less response by the MBDA score relative to those treated with adalimumab despite similar improvements in other clinical measures, suggesting that the mechanism of action of specific DMARDs may influence the MBDA score responsiveness. Whether methotrexate (MTX) treatment, a cornerstone therapy in RA, might similarly influence the convergent validity of the MBDA score, or whether the MBDA score is sufficiently responsive to detect clinical change among RA patients initiating MTX, has not been well elucidated.

While current RA treatment guidelines recommend MTX as the preferred initial agent [6], many patients will not achieve low disease activity with MTX monotherapy [7]. The identification of predictive factors of MTX response/non-response would be an important step in allowing for the personalized selection of optimal therapies earlier in the disease course, hastening the achievement of treatment targets. To date, no clinically useful predictive factors have been identified. The MBDA score previously differentiated response to Triple Therapy (MTX, hydroxychloroquine, and sulfasalazine) vs. tumor necrosis factor inhibitor (TNFi) therapy in a retrospective evaluation of one trial [8]. In this study, patients with a low MBDA score after inadequate response to MTX were more likely to respond to subsequent Triple Therapy, whereas those with a high MBDA score after MTX inadequate response were more likely to respond to TNFi therapy. Whether the MBDA score may also predict MTX treatment response has only been investigated within one trial of early RA patients with moderate-to-high disease activity by DAS28-ESR [9]. In this study, the MBDA score at baseline was similar between those who did/did not achieve low disease activity. The authors derived a four component biomarker score composed of CRP, leptin, TNF-RI, and vascular cell adhesion molecule-1 (VCAM-1) that was associated with achieving low disease activity.

The two objectives of this study were to 1) assess the ability of the MBDA score to predict MTX treatment response and 2) assess the validity and responsiveness of the MBDA score in RA patients initiating MTX.

Patients and Methods

Study design and eligibility criteria

Patients were participants in a 16-week open-label study of predictors of methotrexate response ([ClinicalTrials.gov NCT03414502](https://clinicaltrials.gov/ct2/show/study/NCT03414502)) among sites (n=6) within the Rheumatology and Arthritis Investigational Network (RAIN) who were enrolled from June 2008 through March 2016. Eligible patients were 19 years old, fulfilled 1987 ACR criteria for RA [10], had no exposure to MTX within the last 12 months, were taking no or stable doses of prednisone (≤ 10 mg of prednisone per day or equivalent) for at least 2 weeks, and were taking no or stable doses of non-steroidal anti-inflammatory drugs (NSAIDs) for at least 1 week. Pregnant or lactating women, men and women of childbearing potential not practicing a successful method of contraception, and patients with a history of alcohol abuse who were not willing to limit or abstain from alcohol intake were excluded. Additionally, patients were excluded if significant cytopenias or abnormal liver or renal function tests were present at screening.

Patients initiated oral or subcutaneous MTX at a dose of 15 mg weekly and folic acid 1 mg daily by mouth. At week 8, patients with a DAS28-ESR >2.6 had the MTX dose increased to 20 mg weekly until the end of the study (week 16). All patients provided informed consent and this study received Institutional Review Board approval (University of Nebraska Medical Center).

Data collection

At the baseline visit, age, sex, race, smoking history (smoking status and pack-years), alcohol use, and RA disease duration were recorded. At baseline, week 8, and week 16 visits, the Health Assessment Questionnaire (HAQ) [11], pain scale (0–10 visual analogue scale [VAS]), fatigue scale (0–10 VAS), patient global assessment (PtGA, 0–100 VAS), 28-joint swollen and tender joint counts, and ESR were collected. The DAS28-ESR was calculated from its components as previously described [12]. The study outcomes were the proportion of patients achieving ACR (20, 50, and 70) responses [13, 14], a significant improvement in DAS28-ESR (>1.2 unit reduction) or MBDA score (>8 unit reduction) [15–17], or achieving remission/low disease activity by DAS28-ESR (score ≤ 3.2) at week 16.

Specimen processing and MBDA score measurement

Serum was collected at baseline and week 16 and stored at -70°C until MBDA score measurement. Rheumatoid factor and CRP were measured by nephelometry, and anti-cyclic citrullinated peptide (CCP) antibodies were measured using a 2nd generation enzyme-linked immunosorbent assay. Frozen specimens were transported to Crescendo Bioscience for measurement of the MBDA score, which has been well described previously [2]. Disease activity according to the MBDA score was classified as low (≤ 29), moderate (> 29 and ≤ 44), or high (> 44) [2]. Primary analyses used MBDA scores adjusted for age, sex, and leptin [18], with unadjusted scores examined in secondary analyses.

Statistical analyses

Baseline characteristics were assessed with descriptive statistics. The ability of baseline MBDA scores to predict treatment response at 16 weeks was assessed using multivariable logistic regression models adjusting for age, sex, race, smoking status, HAQ, and anti-CCP antibody positivity, similar to prior work [9]. Using models with the same covariates, we tested whether baseline DAS28-ESR scores were associated with MTX response. We also tested whether the proposed four component biomarker score was predictive of treatment response, using 4 of the 12 markers and cut-off values previously suggested to be predictive of MTX response in patients with RA (CRP 51.5 mg/L, leptin 14.5 microg/L, TNF receptor I [TNF-RI] 1.75 microg/L, vascular cell adhesion molecule 1 [VCAM-1] 0.605 mg/L)^[9].

To assess the performance of the MBDA score in measuring disease activity during MTX treatment, we calculated Pearson's correlations and corresponding 95% confidence intervals of MBDA scores with DAS28-ESR, HAQ, ESR, and PtGA values at baseline and week 16 (convergent validity), as well as the correlations between changes in these parameters (external responsiveness). Pearson's correlation coefficients (r) were classified based on the following cutoffs: very weak (≤ 0.19), weak (0.20 to 0.39), moderate (0.40 to 0.59), strong (0.60 to 0.79), and very strong (≥ 0.80) [19]. Internal responsiveness was determined by evaluating the absolute and percent change in these measures over 16 weeks, as well as by calculating standardized response means (SRMs) to facilitate comparisons between instruments with different scoring ranges. SRMs were considered small for absolute values of 0.20 to 0.49, moderate for values 0.50 to 0.79, and large at 0.80 or greater [20]. Two-sided p values < 0.05 were considered statistically significant, and complete case analysis was used for missing data. All analyses were completed in Stata SE 16.0 (StataCorp).

Results

Study completion and baseline characteristics

Of 130 patients that were enrolled in the study, 114 completed the study, 95 of which had follow-up MBDA scores available (Figure 1). Sixteen patients dropped out of the study, including seven due to toxicity or intolerance, seven that were lost to follow-up, and two withdrew consent. Baseline characteristics of the 130 patients with initial MBDA scores available are shown in Table 1. Characteristics were similar for patients who either did not complete the study or did not have follow-up MBDA scores available except for a lower frequency of Caucasian race (91.6% vs. 74.3%, Supplemental Table 1). The majority of the population was white (86.9%), female (75.4%), and seropositive (72.9% positive for rheumatoid factor, 74.6% positive for anti-CCP). Reflecting the eligibility criteria, participants had high disease activity with a mean DAS28-ESR score of 5.3 (SD 1.2). The majority also had moderate- (28.5%) to-high (60.8%) disease activity by the MBDA score. Mean MBDA score (adjusted for age, sex, and leptin) at study initiation was 50.2 (SD 17.3) and slightly lower for the unadjusted MBDA scores 48.3 (SD 17.2).

Percent achieving treatment response

After 16 weeks of MTX therapy, 48.3% of patients had achieved an ACR20 response, 28.1% achieved an ACR50 response, and 11.4% achieved an ACR70 response (Table 2). There was no statistically significant difference between patients that had improvement in DAS28-ESR compared to the MBDA score (67.9% vs. 54.7%; $P = 0.19$) using previously defined minimum important thresholds [15, 17]. Remission or low disease activity (DAS28-ESR 3.2) was attained in 50.5% of patients.

Prediction of treatment response

When adjusted for age, sex, race, smoking status, anti-CCP antibody positivity, and HAQ, there were no statistically significant associations between higher baseline MBDA scores and achieving ACR20, ACR50, ACR70, or DAS28-ESR low disease activity (Table 3). Findings were similar using the MBDA scores that were not adjusted for age, sex, and leptin (unadjusted MBDA score). We also tested the four component biomarker score proposed by Hambardzumyan et al. [9] that included 4 of the 12 biomarkers as a predictor of MTX treatment response, derived from a sample of 298 patients with RA initiating MTX monotherapy. This four component biomarker score was not significantly associated with treatment response by ACR20, ACR50, ACR70, a significant decrease in DAS28, or low disease activity (Table 3).

Using the same covariates, the baseline DAS28-ESR predicted ACR20 response at week 16 (Table 3, OR 1.89 [95% CI 1.20 – 2.96], $P = 0.006$) and a significant improvement in DAS28 (OR 1.91 [95% CI 1.14 – 3.21], $P = 0.01$). This did not reach statistical significance for a more favorable ACR50 response (OR 1.43 [95% CI 0.90 – 2.28], $P = 0.13$) or ACR70 response (OR 1.45 [95% CI 0.72 – 2.92], $P = 0.30$). Results for the MBDA score and DAS28-ESR were similar when both were entered as predictors into the same multivariable model (Table 3).

Correlation of MBDA score with disease activity measures

We assessed the convergent validity of the MBDA score with other measures of RA disease activity and functional status by calculating correlations at baseline and week 16. There were moderate-to-weak correlations between the MBDA scores and DAS28-ESR at baseline (Table 4, $r = 0.36$ for adjusted MBDA score, $r = 0.44$ for unadjusted MBDA score). At week 16, these correlations were weak ($r = 0.20$ for adjusted MBDA, $r = 0.30$ unadjusted MBDA). There were moderate correlations between the MBDA scores with the ESR at baseline ($r = 0.54$ and 0.59) and week 16 ($r = 0.42$ and 0.51). The MBDA score weak to very weakly correlated with PtGA at baseline ($r = 0.21$ and 0.23) and week 16 ($r = 0.14$ and 0.19). Correlations between the MBDA scores and HAQ at baseline were weak ($r = 0.30$ and 0.34) while at week 16, the MBDA scores correlated weakly to very weakly with HAQ ($r = 0.11$ and 0.23). In contrast, the DAS28-ESR correlated moderately to strongly with HAQ ($r = 0.45$ baseline, $r = 0.63$ week 16).

External responsiveness was assessed through correlations of change in MBDA score with change in other RA measures. Change in MBDA score moderately correlated with change in DAS28-ESR ($r = 0.42$) and change in ESR ($r = 0.46$ and 0.48). Weak correlations were observed between change in MBDA score and change in PtGA ($r = 0.23$ and 0.24) and HAQ ($r = 0.25$). In contrast, changes in DAS28-ESR moderately correlated with changes in HAQ ($r = 0.50$).

Internal responsiveness of MBDA score and DAS28-ESR

Over 16 weeks with MTX treatment, MBDA scores decreased by a mean of 10.4 units (SD 14.7) while DAS28-ESR decreased by 1.9 units (SD 1.5) and the ESR decreased by 17.2 mm/hour (SD 16.5). SRMs were large for DAS28-ESR (1.31), moderate for the MBDA score (0.71), and small for the ESR (0.44). The results for DAS28-ESR were consistent using all individuals with baseline and week 16 DAS28-ESR scores, but excluded from other analyses due to missing follow-up MBDA scores (SRM 1.32).

Discussion

While MTX remains a cornerstone therapy in RA, many patients will not achieve treatment goals on MTX alone [7], and clinical factors capable of accurately predicting treatment response are lacking. Additionally, it is unclear whether MTX treatment may influence the validity of the MBDA score as a measure of RA disease activity as has been suggested with other RA therapies [4]. In this 16-week open-label study of protocolized MTX treatment for active RA, we did not find the MBDA score or the four component biomarker score proposed by Hambardzumyan [9] to be predictive of treatment response after the initiation of MTX. MTX treatment did not substantially influence the validity of the MBDA score as a measure of RA disease activity, with weak-to-moderate correlations with the DAS28-ESR and other measures of RA activity both at baseline and week 16. We found the MBDA score to be moderately responsive to MTX treatment, but less responsive than the DAS28-ESR. These findings are the first to our knowledge to comprehensively characterize the validity, responsiveness, and predictive ability of the MBDA score in patients with RA treated with MTX.

The early aggressive treatment of RA is recommended in major management guidelines [6, 21], with MTX being the recommended first-line RA therapy in active disease. Given many patients will have an inadequate response to MTX monotherapy, there is a need for the identification of factors that may predict MTX response and facilitate earlier escalation or change of therapy when indicated. While the MBDA score's measurement of 12 serum biomarkers was attractive as a potential predictor, we did not find baseline scores to significantly predict MTX treatment response. Similarly, we did not validate the four-component biomarker score utilizing CRP, leptin, TNF-RI, VCAM-1 that was proposed by Hambardzumyan, demonstrating the importance of externally validating novel biomarkers in independent cohorts. Together, our results do not support the regular use of the MBDA score or the four component biomarker score as a predictor of MTX response in RA. Additional research is needed to determine if the MBDA score may predict MTX response in select clinical scenarios and identify other biomarkers/biomarker panels capable of predicting MTX response.

In contrast to the MBDA scores, higher baseline DAS28-ESR scores were significantly associated with ACR20 response and DAS28-ESR response in our study. Baseline DAS28-ESR was not significantly associated with ACR50 or ACR70 responses, which may be related to the limited 16-week follow-up period contributing to fewer ACR50 and ACR70 responses and reduced statistical power. This finding is in line with those by Sergeant et al. [22] who found lower DAS28-CRP scores predicted MTX non-response in a multicenter UK study. Conversely, patients with higher DAS28-ESR scores were non-significantly less likely to achieve remission/low disease activity. Similar findings were previously reported by de Rotte et al. [23]. Our findings illustrate that treatment response outcome measures relying on an absolute magnitude of change, such as ACR response criteria or a DAS change >1.2 units, are more likely to occur with higher baseline disease activity scores. However, treatment response outcomes that assess achieving a disease activity treatment target will favor those with disease activity scores closest to the target disease activity value. Supporting this, Curtis et al. previously demonstrated that clinically important differences in disease activity scores depend on the starting disease activity state [24], with higher absolute changes in scores needed for clinically significant improvement when starting in high disease activity.

Several studies have investigated the validity of the MBDA score by correlating MBDA scores with other RA disease activity measures. While a recent meta-analysis suggests moderate correlation between the MBDA score and other RA disease activity measures [3], individual studies have suggested select therapies could influence the validity of the MBDA score [4]. In this study, we found weak-to-moderate correlations between the MBDA score and DAS28-ESR that did not differ substantially between pre- and post-MTX treatment measures, suggesting MTX treatment does not meaningfully influence the validity of the MBDA score. We also correlated the MBDA score with individual disease activity components and functional status over these same time points. These correlations demonstrated that the MBDA score is more closely associated with acute phase reactants than patient reported measures of RA disease activity. Our findings build upon prior studies which have shown stronger correlations between the MBDA score with RA disease activity measures that include acute phase reactants [3].

Our study is among the first efforts to assess the responsiveness of the MBDA score. Over 16 weeks of protocolized MTX therapy, we calculated a SRM of -0.7 for the MBDA score (moderate responsiveness [20]) and -1.3 for the DAS28-ESR (large responsiveness). External responsiveness testing similarly showed stronger correlations between changes in HAQ with changes in the DAS28-ESR than the MBDA score. Thus, the MBDA score does not appear to be as sensitive to change as the DAS28-ESR. In settings where physical examination is limited and composite disease activity measures such as a DAS28-ESR cannot be calculated (e.g. in telehealth settings[25]), the MBDA score may be a valuable alternative for monitoring treatment response. The MBDA score may be preferred in this setting over the ESR (SRM of -0.4), given its better sensitivity to change. While this study was not a cost-effectiveness analysis, it is important to consider the additional costs related to the MBDA score compared to other RA disease activity measures when evaluating its potential value in clinical practice.

Because this study aimed to assess predictors of MTX treatment response, patients were selected who had active RA. Therefore, we were unable to compare categorization of MBDA scores and DAS28-ESR scores among disease activity states since most had moderate or high disease activity. Correlations between disease activity measures may have varied if patients with lower levels of disease activity were included. However, our results are in line with a previous systematic literature review and meta-analysis [3] summarizing the validity of the MBDA scores. Due to a participant dropout and week 16 blood samples not being available at the time MBDA score measurement was completed on the cohort, 35 patients did not have follow-up MBDA scores. Characteristics of these patients were generally similar to those with complete data, and the responsiveness of the DAS28-ESR among the overall cohort (SRM 1.31) and those with available follow-up MBDA scores (SRM 1.32) was consistent. Among the strengths of the study are the prospective design with protocolized MTX treatment, conduct at multiple centers that improves the generalizability, rigorous biospecimen collection and processing, standardized clinical data collection, and analyses of both MBDA score predictive ability as well as assessments of both validity and responsiveness.

In summary, in a 16-week open-label study of MTX in RA, we found the MBDA score did not significantly predict MTX treatment response. Correlations of the MBDA score with other RA measures (most weak to moderate in strength) were not substantially affected by MTX treatment. The MBDA score was moderately responsive as an instrument for detecting improvement in RA disease activity with MTX treatment, but less responsive than the DAS28-ESR. Further investigation of alternative biomarkers is needed to accurately predict MTX response and guide initial therapy selection in patients with RA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Significance

- Few studies have evaluated whether the multibiomarker disease activity (MBDA) score predicts methotrexate treatment response in patients with RA as well as the validity and responsiveness of the MBDA score during methotrexate treatment.
- The MBDA score demonstrated weak-to-moderate correlations with other measures of RA disease activity that persisted following methotrexate treatment.
- The MBDA score did not predict treatment response in RA patients initiating methotrexate.
- The MBDA score was less responsive than the DAS28-ESR score in detecting clinical change in RA patients following methotrexate treatment.

Figure 1. Study flow diagram.

The multi-biomarker disease activity (MBDA) score was measured on 130 patients participating in an open-label study of methotrexate. A total of 114 patients completed the 16-week study, and serum at week 16 was available for multi-biomarker disease activity score measurement on 95 patients.

Abbreviations: MBDA = Multi-biomarker disease activity score

Table 1.

Baseline characteristics of study population (N = 130)

Variable	Mean (SD) or N (%)
Age, years	54.2 (15.7)
Female sex	98 (75.4%)
Caucasian race	113 (86.9%)
Smoking status	
Current	28 (21.7%)
Former	47 (36.4%)
Never	55 (42.3%)
RA disease duration, months ^a	2.6 (16.2)
RF positive ^b	94 (72.9%)
Anti-CCP positive	97 (74.6%)
28 TJC	10.7 (7.8)
28 SJC	9.4 (5.6)
Pain (0–10)	4.7 (2.3)
Patient global (0–100)	47.3 (23.4)
HAQ	0.80 (0.57)
ESR ^b	27.3 (22.0)
CRP	16.3 (23.0)
DAS28-ESR ^c	5.3 (1.2)
DAS28-CRP	4.9 (1.2)
MBDA score, unadjusted [*]	48.3 (17.2)
MBDA score, adjusted [*]	50.2 (17.3)
MBDA score category, unadjusted [*]	
Low	15 (11.5%)
Moderate	36 (27.0%)
High	79 (60.8%)
MBDA score category, adjusted [*]	
Low	14 (10.8%)
Moderate	37 (28.5%)
High	79 (60.8%)

^a n = 50 missing values;^b n = 1 missing values;^c n = 2 missing values^{*} unadjusted MBDA scores are calculated using the 12 component biomarkers; adjusted MBDA scores are adjusted for age, sex, and leptin

Abbreviations: RA = rheumatoid arthritis; RF = rheumatoid factor; CCP = cyclic citrullinated peptide; TJC = total joint count; SJC = swollen joint count; HAQ = health assessment questionnaire; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = 28-joint disease activity score; MBDA = multi-biomarker disease activity

Table 2.

Percent achieving treatment response criteria.

Response criteria (n included in analysis)	N (%) achieving response
ACR 20 (n=114)	55 (48.3%)
ACR 50 (n=114)	32 (28.1%)
ACR 70 (n=114)	13 (11.4%)
DAS28-ESR MID ^a (n=106)	72 (67.9%)
MBDA score MID ^b (n=95)	52 (54.7%)
DAS28-ESR low disease activity/remission (n=107)	54 (50.5%)

^aDAS28-ESR MID 1.2[15]^bMBDA score MID 8[17]

Abbreviations: ACR = American College of Rheumatology response criteria; DAS28-ESR = 28-joint disease activity score with erythrocyte sedimentation rate; MBDA = multi-biomarker disease activity score; MID = minimum important difference

Table 3.

Ability of the MBDA score and DAS28-ESR to predict treatment response in rheumatoid arthritis patients initiating methotrexate

	ACR20		ACR50		ACR70		DAS >1.2 ^a		Achieve Rem/LDA ^b	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
<i>Adjusted (age, sex, leptin) MBDA Score (n=114)</i>										
MBDA score *	1.23 (0.96, 1.56)	0.10	1.12 (0.86, 1.45)	0.41	1.01 (0.70, 1.47)	0.95	1.28 (0.97, 1.69)	0.08	1.08 (0.84, 1.39)	0.57
<i>Unadjusted MBDA Score (n=114)</i>										
MBDA score *	1.15 (0.91, 1.46)	0.24	1.07 (0.82, 1.38)	0.63	0.95 (0.66, 1.38)	0.79	1.24 (0.95, 1.63)	0.11	1.05 (0.81, 1.34)	0.73
<i>DAS28-ESR (n=113)</i>										
DAS28-ESR *	1.89 (1.20, 2.96)	0.006	1.43 (0.90, 2.28)	0.13	1.45 (0.72, 2.92)	0.30	1.91 (1.14, 3.21)	0.01	0.71 (0.45, 1.14)	0.16
<i>MBDA Score and DAS28-ESR combined in the same model (n=113)</i>										
MBDA score *	1.11 (0.86, 1.44)	0.42	1.04 (0.79, 1.38)	0.77	0.94 (0.64, 1.39)	0.76	1.19 (0.89, 1.59)	0.25	1.17 (0.89, 1.55)	0.26
DAS28-ESR *	1.79 (1.12, 2.86)	0.02	1.40 (0.85, 2.29)	0.19	1.51 (0.71, 3.19)	0.28	1.79 (1.04, 3.06)	0.03	0.65 (0.39, 1.07)	0.09
<i>Four Component Biomarker Score (CRP, leptin, TNF-RI, VCAM-1)[9] (n=114)</i>										
Biomarker Score	1.08 (0.72, 1.61)	0.71	0.89 (0.57, 1.39)	0.61	0.58 (0.28, 1.19)	0.14	1.49 (0.93, 2.39)	0.10	1.29 (0.83, 2.02)	0.26

Multivariable logistic regression models adjusting for age, sex, race, smoking status, anti-CCP positivity, and HAQ.

* Modeled as continuous variables with an MBDA score unit change of 10 and DAS28-ESR unit change of 1

^a n=106 and

^b n=107 included in these analyses

Abbreviations: MBDA = multi-biomarker disease activity; DAS28-ESR = 28-joint disease activity score with erythrocyte sedimentation rate; ACR = American College of Rheumatology response criteria; Rem/LDA = remission or low disease activity by DAS28; OR = odds ratio; CRP = C-reactive protein; TNF-RI = tumor necrosis factor receptor-1; VCAM-1 = vascular cell adhesion molecule-1

Table 4.

Correlation of the MBDA score with disease activity measures in rheumatoid arthritis patients initiating methotrexate.

<i>Convergent validity</i>	DAS28-ESR			ESR			PtGA			HAQ		
	n	r	95% CI	n	r	95% CI	n	r	95% CI	n	r	95% CI
Baseline , MBDA score	128	0.36	(0.20, 0.50)	128	0.54	(0.40, 0.65)	130	0.21	(0.03, 0.36)	130	0.30	(0.14, 0.45)
Week 16 , MBDA score	90	0.20	(−0.01, 0.39)	90	0.42	(0.23, 0.58)	95	0.14	(−0.06, 0.33)	95	0.11	(−0.09, 0.31)
Baseline , unadjusted MBDA score	128	0.44	(0.29, 0.57)	128	0.59	(0.47, 0.70)	130	0.23	(0.06, 0.39)	130	0.34	(0.18, 0.49)
Week 16 , unadjusted MBDA score	90	0.30	(0.10, 0.48)	90	0.51	(0.34, 0.65)	95	0.19	(−0.02, 0.37)	95	0.23	(0.03, 0.41)
Baseline , DAS28-ESR	-	-	-	-	-	-	-	-	-	128	0.45	(0.30, 0.58)
Week 16 , DAS28-ESR	-	-	-	-	-	-	-	-	-	107	0.63	(0.50, 0.73)
<i>External responsiveness</i>	DAS28-ESR			ESR			PtGA			HAQ		
	n	r	95% CI	n	r	95% CI	n	r	95% CI	n	r	95% CI
MBDA score	89	0.42	(0.23, 0.58)	89	0.48	(0.30, 0.62)	95	0.24	(0.04, 0.42)	95	0.25	(0.06, 0.43)
unadjusted MBDA score	89	0.42	(0.23, 0.58)	89	0.46	(0.28, 0.61)	95	0.23	(0.04, 0.42)	95	0.25	(0.05, 0.43)
DAS28-ESR	-	-	-	-	-	-	-	-	-	106	0.50	(0.35, 0.63)

Abbreviations: DAS28 = 28-joint disease activity score; ESR = erythrocyte sedimentation rate; PtGA = Patient global assessment of disease activity; HAQ = health assessment questionnaire; r = correlation coefficient; MBDA = multi-biomarker disease activity; n = number; = change

Table 5.

Responsiveness of the MBDA score and DAS28-ESR in rheumatoid arthritis patients initiating methotrexate

	Baseline Mean (SD)	Week 16 Mean (SD)	Absolute change Mean (SD)	SRM
<i>Among those with baseline and week 16 MBDA scores</i>				
MBDA score (n=95)	50.7 (17.5)	40.3 (13.4)	−10.4 (14.7)	−0.71
Unadjusted MBDA score (n=95)	48.8 (16.9)	39.4 (14.7)	−9.4 (14.5)	−0.65
DAS28-ESR (n=89)	5.3 (1.1)	3.3 (1.3)	−1.9 (1.5)	−1.31
ESR (n=89)	26.2 (19.9)	19.0 (13.5)	−7.2 (16.5)	−0.44

Abbreviations: MBDA=multi-biomarker disease activity; DAS28-ESR= Disease activity score with 28 joint counts with ESR; ESR=erythrocyte sedimentation rate SD=standard deviation; SRM=standardized response mean