BRIEF REPORT

Estimating Disease Activity Using Multi-Biomarker Disease Activity Scores in Rheumatoid Arthritis Patients Treated With Abatacept or Adalimumab

Roy Fleischmann,[1] Sean E. Connolly,[2] Michael A. Maldonado,[2] and Michael Schiff[3]

Objective. To assess the ability of a multi-biomarker disease activity (MBDA) test (Vectra DA) to reflect clinical measures of disease activity in patients enrolled in the AMPLE (Abatacept Versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate) trial.

Methods. In the AMPLE trial, patients with active rheumatoid arthritis (RA) who were naive to biologic agents and had an inadequate response to methotrexate were randomized (1:1) to receive subcutaneous abatacept (125 mg every week) or subcutaneous adalimumab (40 mg every 2 weeks), with background methotrexate, for 2 years. The MBDA score was determined using serum samples collected at baseline, month 3, and years 1 and 2. The adjusted mean change from baseline in the MBDA score was compared between the abatacept and adalimumab treatment groups. Cross-tabulation was used to compare the MBDA score with the following clinical measures of disease activity: Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP), and Routine Assessment of Patient Index Data 3 (RAPID-3).

Results. In total, 318 patients were randomized to receive abatacept, and 328 were randomized to receive adalimumab; MBDA data were available for 259 and 265 patients, respectively. No association between the MBDA score and disease activity defined by the CDAI, SDAI, DAS28-CRP, or RAPID-3 in the abatacept and adalimumab treatment groups was observed.

Conclusion. The MBDA score did not reflect clinical disease activity in patients enrolled in AMPLE and should not be used to guide decision-making in the management of RA, particularly for patients who receive abatacept or adalimumab as the first biologic agent.

[1]Roy Fleischmann, MD: University of Texas Southwestern Medical Center, Dallas; [2]Sean E. Connolly, PhD, Michael A. Maldonado, MD: Bristol-Myers Squibb, Princeton, New Jersey; [3]Michael Schiff, MD: University of Colorado, Denver.

Address correspondence to Roy Fleischmann, MD, Metroplex Clinical Research Center, 8144 Walnut Hill Lane, Dallas, TX 75231. E-mail: rfleischmann@arthdocs.com.

Quantitative assessment of disease activity over time in patients with rheumatoid arthritis (RA) has been accepted as being necessary to guide treatment decisions in clinical practice (1,2). In 2012, the American College of Rheumatology (ACR) recommended 6 disease activity measures for point-of-care clinical use: the Clinical Disease Activity Index (CDAI) (3), Simplified Disease Activity Index (SDAI) (4), Disease Activity Score in 28 joints (DAS28) using the erythrocyte sedimentation rate or the OAS28 using the C-reactive protein level (DAS28-CRP) (5), Routine Assessment of Patient Index Data 3 (RAPID-3) (6), and/or Patient Activity Scale (PAS) and PAS-II (7).

A disease activity scoring method derived from a panel of serum biomarkers could reflect underlying pathophysiologic processes in RA and thereby complement existing clinical measures of disease activity. A multi-biomarker disease activity (MBDA) test (Vectra DA) has been developed that encompasses 12 individual biomarkers: YKL-40 (human cartilage glycoprotein 39), interleukin-6 (IL-6), leptin, tumor necrosis factor receptor I (TNFRI), vascular endothelial growth factor A, epidermal growth factor, vascular cell adhesion molecule 1, serum amyloid A (SAA), matrix metalloproteinase 1 (MMP-1), MMP-3, resistin, and CRP. The MBDA score was formulated to correlate with the DAS28-CRP,

with a range of 0–100 and a higher score corresponding to more severe disease activity (8).

Validation of the MBDA score as a measure of RA disease activity has been performed in patients selected from 3 observational cohorts (9); consequently, the validation cohort may have comprised a population with a broader range of disease activity, disease duration, and prior/concomitant medication than may be expected in a clinical trial setting. The association between changes in the MBDA score and changes in the DAS28-CRP has been assessed in patients with RA initiating treatment with methotrexate (MTX) or anti-TNF agents, and changes in the MBDA score over 12 weeks were loosely correlated with corresponding changes in the DAS28-CRP (r = 0.56 and r = 0.43 in anti–cyclic citrullinated peptide and/or rheumatoid factor seropositive and double-seronegative patients, respectively) (9). Further studies in patients receiving anti-TNF agents and/ or conventional synthetic disease-modifying antirheumatic drugs (DMARDs) showed that the MBDA score again was loosely correlated with clinical measures of disease activity in these patient groups (10–12). In contrast, it has previously been noted that the MBDA score may underestimate the clinical response to tocilizumab (an anti–IL-6 agent) due to treatment-associated increases in serum IL-6 levels (13).

The AMPLE (Abatacept versus Adalimumab Comparison in Biologic-Naive RA Subjects with Background Methotrexate; ClinicalTrials.gov identifier: NCT 00929864) study was a 2-year, phase IIIb, multinational, prospective, randomized, head-to-head study comparing the efficacy and safety of subcutaneous abatacept with that of subcutaneous adalimumab, both on background MTX, in biologic agent–naive patients with active RA and an inadequate response to MTX (14). Abatacept and adalimumab were similarly effective over 2 years, based on a variety of clinical as well as functional and radiographic outcomes (14,15). In the AMPLE study, disease activity was assessed using a range of clinical measures, including the DAS28-CRP, CDAI, and SDAI, making this a suitable study in which to evaluate the correlation of the MBDA score with disease activity. The objective of this post hoc analysis was to assess the ability of the MBDA score to estimate disease activity in patients in the AMPLE study who received abatacept or adalimumab over 2 years.

PATIENTS AND METHODS

Patient population. The AMPLE study included adult biologic agent–naive patients who met the ACR 1987 revised criteria for the classification of RA (16), had a confirmed diagnosis of RA for ≤5 years, and in whom the response to MTX was inadequate. At the time of randomization, patients were required to have a DAS28-CRP of ≥3.2 and a history of anti–cyclic citrullinated peptide or rheumatoid factor seropositivity or (if seronegative) an elevated erythrocyte sedimentation rate or CRP level.

Study design. The AMPLE study design, including details of ethics approvals, has been reported previously (14). Briefly, patients were randomized (1:1) to receive subcutaneous abatacept (125 mg weekly without an intravenous loading dose) or adalimumab (40 mg every 2 weeks), both with background MTX (15–25 mg/week, or ≥7.5 mg/week in patients with documented intolerance).

Efficacy assessments for this post hoc analysis included the DAS28-CRP, CDAI, SDAI, and RAPID-3 at baseline, month 3, year 1, and year 2. Scores were categorized as remission, low disease activity (LDA), moderate disease activity (MDA), or high disease activity (HDA) for the CDAI, SDAI, and RAPID-3, and as <2.6, 2.6 to <3.2, 3.2–5.1, or >5.1 for the DAS28-CRP (7).

Biomarker levels were measured in serum samples collected at baseline, month 3, year 1, and year 2 (performed at Crescendo Bioscience). MBDA scores, provided by the manufacturer and calculated using the published algorithm (8), were categorized using the following manufacturer-established cutoff values: LDA <30, MDA 30–44, and HDA >44 (8).

The AMPLE study was conducted in accordance with the Declaration of Helsinki and was consistent with the International Conference on Harmonisation and Good Clinical Practice. The study protocol was approved by the institutional review boards and independent ethics committees at the participating sites.

Statistical analysis. The adjusted mean changes from baseline in the MBDA score at month 3, year 1, and year 2 were calculated for the abatacept and adalimumab groups for all randomized and treated patients with available MBDA data. The adjusted differences and corresponding 95% confidence intervals (95% CIs) in the mean change from baseline in the MBDA score between the abatacept and adalimumab groups were calculated; adjustment was based on an analysis of covariance model with treatment as a factor and baseline MBDA values and DAS28-CRP stratification as covariates.

Cross-tabulation of disease activity classification as defined by the DAS28-CRP, CDAI, SDAI, and RAPID-3 and that based on the MBDA score was performed at baseline, month 3, year 1, and year 2. The percentages of patients without radiographic progression (defined as change from baseline in the total score less than or equal to the smallest detectable change) at year 1 and year 2 were calculated for all randomized and treated patients with available data, stratified by CDAI classification and MBDA score classification.

RESULTS

Patient disposition and baseline characteristics. In the AMPLE study, 646 patients were randomized and treated (318 patients were randomized to the abatacept group, and 328 patients were randomized to the adalimumab group); year 2 was completed by 252 patients and 245 patients, respectively. MBDA data were available for
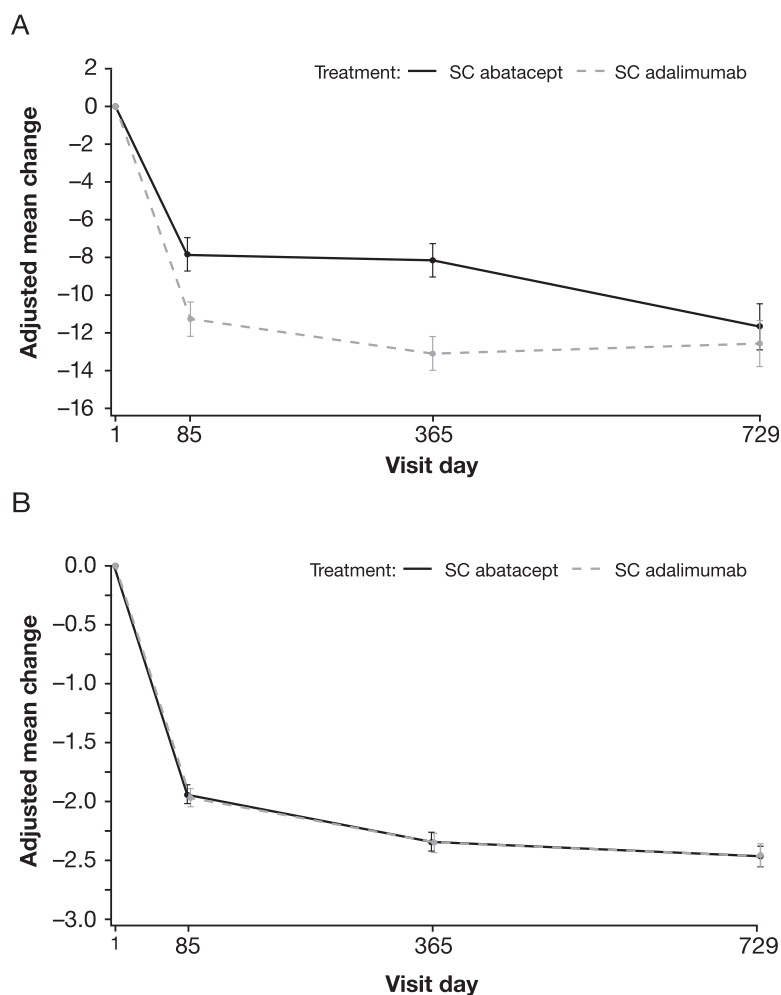
Figure 1. Adjusted mean changes from baseline over time in the multi-biomarker disease activity (MBDA) score (**A**) and the Disease Activity Score in 28 joints using the C-reactive protein value (**B**) for all randomized and treated patients for whom an MBDA score was available. The last observation carried forward approach was used. Horizontal bars show the 95% confidence interval. SC = subcutaneous.

259 patients in the abatacept group and 265 patients in the adalimumab group.

The baseline demographics and disease characteristics of the study population have been reported previously (14). Briefly, the mean age was ~51 years in both arms, the mean disease duration was 1.9 years in the abatacept group and 1.7 years in the adalimumab group, and the mean DAS28-CRP was 5.5 in both arms. The baseline demographics and disease characteristics of patients with available MBDA data were consistent with those of the overall AMPLE study population for both the abatacept and adalimumab groups.

Clinical efficacy. Among patients with MBDA data, the percentage achieving distinct states of remission or LDA (not including remission) after 2 years of treatment was similar in the abatacept and adalimumab groups across clinical measures of disease activity: for

CDAI-defined remission, 36.4% versus 34.1%; for CDAI-defined LDA, 29.5% versus 31.0%; for SDAI-defined remission, 35.6% versus 35.7%; for SDAI-defined LDA, 30.3% versus 28.6%; for a DAS28-CRP of <2.6, 53.0% versus 52.0%; for a DAS28-CRP of 2.6 to <3.2, 11.4% versus 15.0%; for RAPID-3–defined remission, 35.1% versus 24.6%; and for RAPID-3–defined LDA, 19.1% versus 26.2% for abatacept and adalimumab, respectively (Table 1).

Multi-biomarker disease activity. At baseline, the mean ± SD MBDA scores for HDA were 49.7 ± 16.7 in the abatacept group and 51.0 ± 15.5 in the adalimumab group. There was marked discordance in the mean change (improvement) in the MBDA score from baseline over 2 years for both abatacept and adalimumab (Figure 1A) compared with clinical disease activity measures (Figure 1B). For abatacept and adalimumab,

Table 1. Classification of disease activity over time according to clinical disease activity measure and treatment group*

Disease activity measure	Baseline		Month 3		Year 1		Year 2	
	Abatacept	Adalimumab	Abatacept	Adalimumab	Abatacept	Adalimumab	Abatacept	Adalimumab
DAS28-CRP								
No. of patients assessed	241	251	173	174	187	190	132	127
<2.6	2 (0.8)	1 (0.4)	55 (31.8)	49 (28.2)	85 (45.5)	83 (43.7)	70 (53.0)	66 (52.0)
2.6 to <3.2	6 (2.5)	6 (2.4)	23 (13.3)	30 (17.2)	31 (16.6)	32 (16.8)	15 (11.4)	19 (15.0)
3.2–5.1	81 (33.6)	79 (31.5)	68 (39.3)	72 (41.4)	59 (31.6)	62 (32.6)	39 (29.5)	31 (24.4)
>5.1	152 (63.1)	165 (65.7)	27 (15.6)	23 (13.2)	12 (6.4)	13 (6.8)	8 (6.1)	11 (8.7)
CDAI								
No. of patients assessed	240	251	173	172	188	190	132	126
Remission	0 (0)	1 (0.4)	21 (12.1)	22 (12.8)	50 (26.6)	47 (24.7)	48 (36.4)	43 (34.1)
LDA	3 (1.3)	4 (1.6)	57 (32.9)	52 (30.2)	71 (37.8)	69 (36.3)	39 (29.5)	39 (31.0)
MDA	34 (14.2)	31 (12.4)	51 (29.5)	59 (34.3)	45 (23.9)	52 (27.4)	33 (25.0)	24 (19.0)
HDA	203 (84.6)	215 (85.7)	44 (25.4)	39 (22.7)	22 (11.7)	22 (11.6)	12 (9.1)	20 (15.9)
SDAI								
No. of patients assessed	240	251	173	172	187	190	132	126
Remission	0 (0)	1 (0.4)	25 (14.5)	24 (14.0)	48 (25.7)	49 (25.8)	47 (35.6)	45 (35.7)
LDA	3 (1.3)	4 (1.6)	55 (31.8)	53 (30.8)	74 (39.6)	69 (36.3)	40 (30.3)	36 (28.6)
MDA	49 (20.4)	45 (17.9)	56 (32.4)	62 (36.0)	48 (25.7)	54 (28.4)	35 (26.5)	29 (23.0)
HDA	188 (78.3)	201 (80.1)	37 (21.4)	33 (19.2)	17 (9.1)	18 (9.5)	10 (7.6)	16 (12.7)
RAPID-3								
No. of patients assessed	234	249	169	171	185	188	131	122
Remission	3 (1.3)	5 (2.0)	36 (21.3)	29 (17.0)	56 (30.3)	46 (24.5)	46 (35.1)	30 (24.6)
LDA	6 (2.6)	3 (1.2)	29 (17.2)	24 (14.0)	33 (17.8)	34 (18.1)	25 (19.1)	32 (26.2)
MDA	27 (11.5)	29 (11.6)	49 (29.0)	54 (31.6)	53 (28.6)	61 (32.4)	23 (17.6)	27 (22.1)
HDA	198 (84.6)	212 (85.1)	55 (32.5)	64 (37.4)	43 (23.2)	47 (25.0)	37 (28.2)	33 (27.0)
MBDA								
No. of patients assessed	245	251	174	174	189	190	133	127
LDA	36 (14.7)	16 (6.4)	34 (19.5)	48 (27.6)	40 (21.2)	45 (23.7)	27 (20.3)	31 (24.4)
MDA	51 (20.8)	79 (31.5)	66 (37.9)	75 (43.1)	62 (32.8)	92 (48.4)	56 (42.1)	51 (40.2)
HDA	158 (64.5)	156 (62.2)	74 (42.5)	51 (29.3)	87 (46.0)	53 (27.9)	50 (37.6)	45 (35.4)

* All medication was administered subcutaneously. For the Clinical Disease Activity Index (CDAI), remission was defined as a score of ≤2.8, low disease activity (LDA) as a score of >2.8 to ≤10, moderate disease activity (MDA) as a score of >10 to ≤22, and high disease activity (HDA) as a score of >22. For the Simplified Disease Activity Index (SDAI), remission was defined as a score of ≤3.3, LDA as a score of >3.3 to ≤11, MDA as a score of >11 to ≤26, and HDA as a score of >26. For the Routine Assessment of Patient Index Data 3 (RAPID-3), remission was defined as a score of ≤1, LDA as a score of >1 to ≤2, MDA as a score of >2 to ≤4, and HDA as a score of >4. For multi-biomarker disease activity (MBDA), LDA was defined as a score of <30, MDA as a score of 30–44, and HDA as a score of >44. Except where indicated otherwise, values are the number (%). DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein value.

respectively, the adjusted mean changes from baseline in the MBDA score were −7.84 versus −11.25 at month 3, −8.15 versus −13.09 at year 1, and −11.66 versus −12.54 at year 2. The adjusted differences in the mean change from baseline in MBDA scores for abatacept versus adalimumab were 3.41 (95% CI 0.94, 5.88) at month 3, 4.95 (95% CI 2.56, 7.33) at year 1, and 0.89 (95% CI −2.35, 4.12) at year 2.

Correlation between multi-biomarker disease activity and clinical outcomes. At baseline, most patients had MDA or HDA according to both clinical measures and the MBDA score: 98.8% (CDAI), 98.8% (SDAI), 96.7% (DAS28-CRP ≥3.2), 96.2% (RAPID-3) versus 85.3% (MBDA) in the abatacept arm, and 98.0% (CDAI), 98.0% (SDAI), 97.2% (DAS28-CRP ≥3.2), 96.8% (RAPID-3) versus 93.6% (MBDA) in the adalimumab arm (Table 1). At subsequent time points, the percentages of patients with MBDA-defined LDA, MDA, or HDA were inconsistent with the percentages associated

with validated clinical measures of disease activity (Table 1). The CDAI is considered to be an accurate, stringent measure of disease activity (7); however, there was no association between CDAI-defined disease activity and the MBDA score at subsequent time points for either treatment (Figure 2; see also Supplementary Table 1 and Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39714/abstract). For example, at both year 1 and year 2, across both treatment groups, many patients with CDAI-defined remission or LDA had MBDA-classified HDA (Figure 2B; see also Supplementary Figure 1). Similarly, there was no association between disease activity as defined by the DAS28-CRP, SDAI, or RAPID-3 and the MBDA score for either treatment (Figure 2; see also Supplementary Tables 2 and 3 and Supplementary Figure 1, available on the Arthritis & Rheumatology web site at http://online library.wiley.com/doi/10.1002/art.39714/abstract).
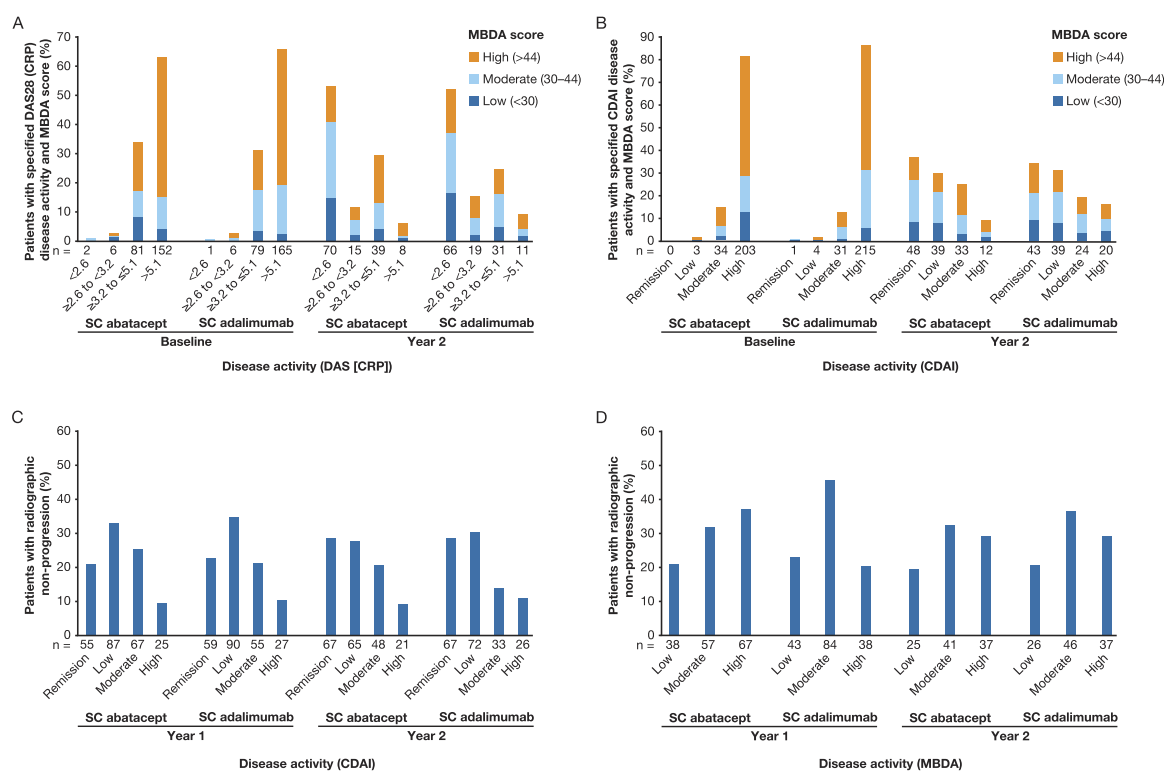
Figure 2. **A** and **B,** Comparison of clinical measures of disease activity and MBDA score categories, for the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) (**A**) and the Clinical Disease Activity Index (CDAI) (**B**), at baseline and year 2. **C** and **D,** Comparison of disease activity as assessed using the CDAI (**C**) and the MBDA score (**D**) in patients with radiographic nonprogression, at years 1 and 2. For the CDAI, remission was defined as a score of ≤2.8, low disease activity (LDA) as a score of >2.8 to ≤10, moderate disease activity (MDA) as a score of >10 to ≤22, and high disease activity (HDA) as a score of >22. For MBDA, LDA was defined as a score of <30, MDA as a score of 30–44, and HDA as a score of >44. Radiographic nonprogression was defined as change from baseline in the total score less than or equal to the smallest detectable change. See Figure 1 for other definitions.

Correlation between clinical efficacy and multi-biomarker-defined disease activity and status of radiographic progression. In both treatment groups, radiographic nonprogression at years 1 and 2 was most common in patients with CDAI-defined remission or LDA and least common in patients with HDA (Figure 2C; see also Supplementary Table 4, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39714/abstract). In contrast, MBDA-defined disease activity did not reflect the status of radiographic progression, which further demonstrated the inconsistency between the MBDA test and validated clinical measures (Figure 2D; see also Supplementary Table 5, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39714/abstract).

DISCUSSION

The MBDA test described herein is available to physicians in the US for the assessment of disease activity in adult patients with RA. The MBDA score has been postulated to be a generally reliable measure of disease activity in patients receiving conventional synthetic DMARDs and/or anti-TNF agents (9–12). However, in the current study, no clear association was observed between MBDA scores and commonly used and validated clinical measures of disease activity over 2 years, regardless of the level of disease activity (remission, LDA, MDA, or HDA) or treatment (abatacept or the anti-TNF agent adalimumab). Additionally, there was a clinically significant disparity in the proportion of radiographic nonprogressors with HDA defined by the MBDA score versus the CDAI, further emphasizing that the MBDA score may not provide information consistent with that provided by validated clinical measures.

A range of measures are available for the assessment of disease activity in routine clinical practice (7); however, it is hoped that a biomarker panel may complement clinical assessment by providing additional insight into underlying RA pathophysiology. Such an assay may

provide a quantitative measure of RA disease activity against which the effect of subsequent interventions can potentially be measured (i.e., response to therapy), thereby aiding physicians in making patient-specific decisions for the management of RA. It is therefore important to establish whether the MBDA test itself is a biomarker panel that can strongly correlate with clinical disease activity scores for individual RA treatments.

Data evaluating the MBDA in patients treated with abatacept are limited. In a previous analysis from the ASSET trial (Impact of Intravenous Abatacept on Synovitis, Osteitis and Structural Damage in Patients with Rheumatoid Arthritis and an Inadequate Response to Methotrexate; a randomized, controlled trial), reported in an abstract only, in which patients with an inadequate response to MTX were randomized (1:1) to receive abatacept or placebo, both on background MTX, those randomized to receive abatacept had greater improvements in the DAS28-CRP and MBDA scores compared with those who received placebo (17). Using pooled data from the abatacept and placebo groups, a modest but statistically significant correlation was identified between clinical disease activity (DAS28-CRP) and the MBDA score over the first month of the study (r = 0.47, $P < 0.001$); however, this correlation was not assessed at later time points (17). Furthermore, a significant association between a European League Against Rheumatism–defined good response (18) at week 16 and change in the DAS28-CRP over the first month of the study ($P = 0.02$) was observed, whereas the association with change in MBDA score over this time period was marginally significant ($P = 0.05$). Because these data were reported in abstract form only, it is difficult to assess the relevance of the correlation between the DAS28-CRP and the MBDA score at 1 month and the predication of subsequent events.

In the current (larger) comparative analysis, improvements in the MBDA score over 2 years differed somewhat between adalimumab and abatacept at month 3 and year 1 (but not at year 2) despite comparable efficacy across clinical measures of disease activity, including inhibition of radiographic progression. Although differences in MBDA score–defined improvement for adalimumab versus abatacept were statistically significant at month 3 and year 1, it is unclear whether the differences of ~3 units at month 3 and 5 units at year 1 are clinically significant. In addition, the mean improvement in the MBDA score over 2 years of ~12 units in both the abatacept and adalimumab groups indicated that most patients still had MDA at year 2, as measured by the MBDA score, regardless of the treatment received, and yet had remission or LDA based on clinical measures. At year 2, most patients in both treatment groups had not

shown radiographic progression, with a reasonably even distribution of ~20–35% (depending on the medication) of nonprogressors falling into each MBDA category, including HDA. In contrast, most patients had achieved at least CDAI-defined LDA, with very few patients showing radiographic progression, irrespective of treatment.

Differences in the MBDA profile for non–anti-TNF biologic agents versus anti-TNF agents were previously observed, including a small study of tofacitinib (a JNK inhibitor) and a study of tocilizumab (an anti–IL-6 agent) (13,19). In the study of 37 patients with RA who were treated with tofacitinib, a statistically significant increase in the leptin level over 1 year was observed. In that study, the MBDA score captured the overall effect of tofacitinib on RA disease activity; however, the effect of tofacitinib on the leptin level requires further clarification (19). In a subanalysis of the ACT-RAY study (Clinical Trials.gov identifier: NCT00810199), the MBDA score underestimated the clinical response to tocilizumab as measured by the DAS28-CRP and CDAI over 24 weeks, in accordance with substantial increases in measured IL-6 concentrations countering decreases in CRP, SAA, and other biomarkers (13). Taken together, these findings highlight the need for cautious interpretation of MBDA scores in the context of all available clinical information.

Prospective data comparing clinical outcomes assessed using the MBDA score with those assessed using ACR-recommended measures (7) are needed to determine whether assessment using the MBDA test can enhance disease management. In the present study, the MBDA score did not reflect disease activity as measured using the CDAI, SDAI, DAS28-CRP, or RAPID-3 in patients treated with abatacept or adalimumab, indicating that assessment using the MBDA test may be of limited value for evaluating outcome in the clinical setting. In this study, the lack of association between clinical or radiographic measures of disease activity and the MBDA score for both abatacept and adalimumab conflicts with previous findings for anti-TNF agents (9,11,12). Of note, the patient population included in the AMPLE trial differs from the original MBDA validation cohort (9). Patients enrolled in the AMPLE study were naive to biologic therapy, had an inadequate response to MTX, moderate-to-severe disease activity, and a mean disease duration of <2 years and were systematically followed up for 2 years. In contrast to patients in the AMPLE study, the MBDA validation cohorts included patients who were older and had less-active disease (lower median DAS28-CRP and patient global assessment of disease activity), and were selected from 3 prospective studies encompassing a range of prior treatment patterns and assessed over only 6–12 weeks (9).

Limitations of this study include the lack of available MBDA data for some patients who participated in the AMPLE trial. The findings presented here should be interpreted in the context of this being a post hoc analysis and only as it pertains to the utility of the MBDA test to serve as a measurement of RA disease activity.

In conclusion, MBDA scores did not reflect disease activity as assessed by radiographic nonprogression or using the CDAI, SDAI, DAS28-CRP, or RAPID-3 in patients treated with abatacept or adalimumab in the AMPLE trial. These findings indicate that the MBDA score should not be used to guide RA management decisions, particularly in patients treated with abatacept or adalimumab as a first biologic agent. Treatment decisions in RA should be based on clinical judgment, utilizing the disease activity measures recommended by the ACR for point-of-care clinical use.

ACKNOWLEDGMENTS

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 published. Dr. Fleischmann 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. Fleischmann, Connolly, Maldonado, Schiff.
Acquisition of data. Fleischmann, Connolly, Maldonado, Schiff.
Analysis and interpretation of data. Fleischmann, Connolly, Maldonado, Schiff.

ROLE OF THE STUDY SPONSOR

REFERENCES

1. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016; 68:1–25.
2. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.
3. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–806.
4. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A Simplified Disease Activity Index for rheumatoid arthritis for use in clinical practice. Rheumatology (Oxford) 2003;42:244–57.
5. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
6. Pincus T, Yazici Y, Bergman M, Maclean R, Harrington T. A proposed continuous quality improvement approach to assessment and management of patients with rheumatoid arthritis without formal joint counts, based on quantitative Routine Assessment of Patient Index Data (RAPID) scores on a Multidimensional Health Assessment Questionnaire (MDHAQ). Best Pract Res Clin Rheumatol 2007;21:789–804.
7. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken) 2012;64:640–7.
8. 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.
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 (Hoboken) 2012;64:1794–803.
10. 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.
11. 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 (Oxford) 2013;52:1202–7.
12. Hirata S, Li W, Defranoux N, Cavet G, Bolce R, Yamaoka K, et al. A multi-biomarker disease activity score tracks clinical response consistently in patients with rheumatoid arthritis treated with different anti-tumor necrosis factor therapies: a retrospective observational study. Mod Rheumatol 2015;25:344–9.
13. Reiss WG, Devenport JN, Low JM, Wu G, Sasso EH. Interpreting the multi-biomarker disease activity score in the context of tocilizumab treatment for patients with rheumatoid arthritis. Rheumatol Int 2016;36:295–300.
14. Schiff M, Weinblatt ME, Valente R, van der Heijde D, Citera G, Elegbe A, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis 2014;73:86–94.
15. Fleischmann R, Schiff M, Weinblatt ME, Maldonado M, Massarotti E, Yazici Y. Two-year results from the AMPLE trial: low disease activity and association between remission and changes in physical function and radiographic outcomes with subcutaneous abatacept or adalimumab [abstract]. Arthritis Rheum 2013;65 Suppl:476.
16. 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.
17. Haney D, Cavet G, Durez P, Alten R, Burmester G, Tak P, et al. Correlation of a multi-biomarker disease activity response assessment to Disease Activity Score 28 (C-reactive protein) response assessment and OMERACT RAMRIS Scores in a placebo-controlled rheumatoid arthritis clinical trial with abatacept (ASSET) [abstract]. Arthritis Rheum 2012;64 Suppl:S913.
18. Van Gestel AM, Prevoo ML, van't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis: comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. Arthritis Rheum 1996;39:34–40.
19. Yamaoka K, Kubo S, Li W, Sonomoto K, Hirata S, Sasso EH, et al. Effects of tofacitinib on leptin and other components of the multi-biomarker disease activity score in patients with rheumatoid arthritis [abstract]. Ann Rheum Dis 2014;73: Suppl:507–8.