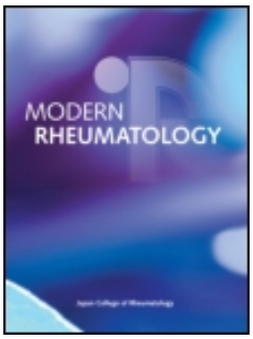

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ORIGINAL ARTICLE

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

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Abstract

Objectives. To assess the ability of a multi-biomarker disease activity (MBDA) score to track clinical response in patients with rheumatoid arthritis (RA) treated with different TNF inhibitors.
Methods. The study included 147 patients who had received adalimumab, etanercept, or infliximab for a year or more, during routine clinical care at the University Hospital of Occupational and Environmental Health, Japan. MBDA scores and clinical measures of disease activity were evaluated at baseline and, after 24 weeks ($N = 84$) and 52 weeks of treatment. Relationships between the changes (Δ) in MBDA score and changes in clinical measures or EULAR response categories were evaluated.
Results. The median disease activity was 5.7 by DAS28-ESR and 64 by MBDA score at baseline, and decreased significantly with treatment. ΔMBDA scores over 1 year correlated with ΔDAS28-ESR ($r = 0.48$) and ΔDAS28-CRP ($r = 0.46$). Linear relationships between ΔMBDA scores and ΔDAS28-ESR or ΔDAS28-CRP were not significantly different between TNF inhibitors. The MBDA scores declined significantly more in good responders (median change: −29) than moderate (–21), and more in moderate than in non-responders (+ 2), by the EULAR criteria.
Conclusions. MBDA scores tracked disease activity and treatment response in patients with RA treated with three TNF inhibitors. The relationships between ΔMBDA scores and ΔDAS28-ESR or ΔDAS28-CRP were consistent across the three TNF inhibitor groups.

Keywords

Biomarkers, Disease activity, Rheumatoid arthritis, TNF inhibitor

History

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Introduction

The treatment goals for patients with rheumatoid arthritis (RA) are to achieve and maintain clinical remission, thereby improving patient outcomes and preventing long-term joint damage and disability. Regular quantitative assessments of disease activity have been shown to play an important role in achieving these goals. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have recommended regular assessment [1–5] using composite clinical measures, including the Disease Activity Score (DAS) [6–8], the modified Disease Activity Score-28 (DAS28) [7,9], the Simplified Disease Activity Index (SDAI) [10], and the Clinical Disease Activity Index (CDAI) [11,12]. Patient-reported outcomes such as the Routine Assessment of Patient Index Data 3 (RAPID3) have also been proposed [13]. These tools include formal or informal joint counts and global assessments by the patient or the assessor, and are all, to some degree, subjective. They are influenced by the expertise of the assessor and are subject to inter- and intra-observer variability [14,15].

By contrast, biomarker-based scoring systems of disease activity have the potential advantages of being objective, independent of assessor expertise, and easy to use in clinical practice [16]. Although no single biomarker has been identified to adequately assess RA disease activity, a multi-biomarker disease activity (MBDA) blood test has been developed and validated [5,17]. The MBDA score has been shown to correlate significantly with clinical disease activity measures (DAS28 with erythrocyte sedimentation rate [DAS28-ESR], DAS28 with C-reactive protein [DAS28-CRP], SDAI, and CDAI) and the Health Assessment Questionnaire Disability Index (HAQ-DI), in both seronegative and seropositive patients [17–19]. The MBDA score has also been shown to track disease activity in treated patients, to distinguish changes in disease activity for patients stratified by EULAR response criteria, and to reflect dose effects in patients treated with mavrilimumab [18–20]. In addition, remission or low disease activity defined by the MBDA score has been associated with limited radiographic progression in patients with early

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RA or established RA during treatment with disease-modifying anti-rheumatic drugs (DMARDs) [21,22].

It is important that a disease activity scoring system performs consistently for patients being treated with different therapies so that the interpretation of its scores can be straightforward. The overall association between changes in MBDA scores and clinical response has been reported for a cohort comprised of patients treated with different therapeutic modalities including methotrexate [MTX] [17]. However, the specific impact of different tumor necrosis factor (TNF) inhibitors on the MBDA score has not been fully investigated. The 2008 ACR guidelines recommend the use of the TNF inhibitors adalimumab [ADA], etanercept [ETN], and infliximab [IFX] in combination with MTX, for patients with long-standing RA with inadequate response to MTX treatment [23]. The purpose of this study was to evaluate changes (Δ) in the MBDA score in relation to the changes of composite clinical disease activity measures and the EULAR response, in a retrospective cohort of Japanese patients with RA treated with ADA, ETN or IFX as part of their standard care in clinical practice.

Patients and methods

Patient cohort

A total of 147 patients previously diagnosed with RA (ACR 1987 criteria), who had been followed for their care at the University of Occupational and Environmental Health, Japan (UOEH), from 2003 through 2010, were selected for this study. These patients were required to have received TNF inhibitor treatment for a minimum of 1 year during that period and to have serum samples available for the present study at baseline (prior to initiating biologic treatment) and 52 weeks after treatment initiation. To meet the criteria of the Japan College of Rheumatology for initiation of anti-TNF therapy [24], patients had to have received more than 3 months of conventional non-biologic DMARD therapy and to have (i) Tender Joint Count-28 (TJC-28) ≥ 6 and Swollen Joint Count-28 (SJC-28) ≥ 6 with either CRP ≥ 2 mg/dL or ESR ≥ 28 mm/hr, or (ii) evidence of progression of joint destruction (bone erosion/joint space narrowing) on imaging, and/or DAS28 ≥ 3.2.

The selected patients had received either ADA (patients treated from 2008 through 2010), ETN (2006–2010), or IFX (2005–2010), each in combination with MTX or as monotherapy if appropriate for the patient. Patients receiving concomitant MTX treatment had received a stable dose for at least 1 month prior to initiating anti-TNF therapy, with a majority being on stable MTX for at least 3 months. This study included the 49 most recent patients in each TNF inhibitor group who met the inclusion criteria. For two patients who had received 2 different TNF inhibitors, each for a course of 1 year, a single period of therapy was randomly chosen and used for all analyses.

This study was performed under the approval of the ethics committee of the UOEH and carried out in compliance with the Helsinki Declaration. Written informed consent was obtained from all participants.

Serum samples and clinical assessments

A total of 378 serum samples from 147 patients were analyzed: 147 from baseline, 84 from week 24 and 147 from week 52. Serum samples had been stored at −40°C at UOEH after collection and at −70°C after transfer to Crescendo Bioscience until biomarker serum concentration testing. Week 24 samples were available for only a subset of patients; their availability was independent of patient disease status.

Clinical assessments included TJC-28, SJC-28, patient global assessment (PGA), and physician global assessment, and were obtained at baseline, week 24, and week 52.

DAS28-ESR, DAS28-CRP, SDAI, and CDAI were derived from available clinical and laboratory data. Physician global assessment data, and therefore CDAI and SDAI, were only available for study visits after 2007. Thus, baseline CDAI and SDAI were available for 87 patients, of whom 75 had SDAI and CDAI at both baseline and 52 weeks.

MBDA score calculation

MBDA scores were generated in the research and development laboratory of Crescendo Bioscience, Inc., (South San Francisco, CA, USA) using the same algorithm as the Vectra® DA test, which combines the concentrations of 12 biomarkers (vascular cell adhesion molecule-1 [VCAM-1], epidermal growth factor [EGF], vascular endothelial growth factor-A [VEGF-A], interleukin [IL]-6, tumor necrosis factor-receptor type 1 [TNF-RI], matrix metalloproteinase [MMP]-1, MMP-3, cartilage glycoprotein 39 [YKL-40], leptin, resistin, serum amyloid A [SAA], and CRP), to generate an integer score from 1 to 100 [5]. Quantification of the 12 biomarkers was performed using an electrochemiluminescence-based multiplexed immunoassay with the Meso Scale Discovery MULTI-ARRAY® platform [25]. Categories of MBDA scores have been defined as low (<30), moderate (30–44), and high (>44) [17].

Statistical analysis

Baseline characteristics were compared across the three groups receiving different TNF inhibitors using the Kruskal-Wallis test (for continuous variables) or Fisher's Exact Test (for categorical variables).

Spearman's rank correlation coefficients (Spearman's r) were calculated to evaluate the correlation between ΔMBDA scores and the change of clinical disease activity indices: ΔDAS28-ESR, ΔDAS28-CRP, ΔSDAI, and ΔCDAI, from baseline to week 52.

Analysis of covariance (ANCOVA) was performed on the changes in disease activity scores from baseline to week 52 to evaluate whether the linear relationships between ΔMBDA scores and ΔDAS28-ESR, or ΔDAS28-CRP, differed between TNF inhibitors. More specifically, the analysis examined whether the expected changes in ΔDAS28-ESR (or ΔDAS28-CRP) corresponding to a 1-unit change in ΔMBDA score would differ between patients treated with different TNF inhibitors. To this effect, linear models (ANCOVA) were fitted with the change in the composite clinical disease activity measure as the response variable, and the ΔMBDA score, type of TNF inhibitor, and interaction between ΔMBDA score and type of TNF inhibitor as explanatory variables. These analyses generated a regression line for each TNF inhibitor group, describing the relationship between ΔDAS28-ESR (or ΔDAS28-CRP) and the ΔMBDA score. An F-test was performed to compare the slopes of these regression lines across the 3 treatment groups simultaneously, by testing whether the coefficients of the interaction terms were equal to 0. When the F-test showed non-significant results, t-tests were also performed to confirm, in pairwise comparisons, that there were also no significant differences between the slopes; these analyses provided additional information to the F-test.

The difference in ΔMBDA score from baseline to week 52 between patient groups defined by level of EULAR response (none, moderate, good) at week 52 was assessed by the Wilcoxon rank-sum test.

All reported p-values are from two-sided tests, and no adjustments were applied for multiple hypothesis testing; p-values <0.05 were considered significant. All statistical analyses were performed using the package R 2.15.1 (www.r-project.org).

Table 1. Patient characteristics at baseline.

	Adalimumab	Etanercept	Infliximab	Total
Number of patients	49	49	49	147
Categorical variable	%	%	%	%
Gender (% female)	88	86	80	84
RF status (% positive)	86	85	86	86
Concomitant use of MTX (%)*	98	61	100	86
Continuous variable	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Age (years)*	64 (55–68)	61 (54–69)	55 (42–64)	60 (50–68)
RA duration (months)*	48 (15–156)	108 (26–240)	47 (15–108)	60 (18–168)
MTX dose[a] (mg/week)*	9 (8–12)	8 (8–10)	8 (8–10)	8 (8–10)
TJC-28	6 (3–13)	8 (4–14)	8 (4–16)	8 (4–15)
SJC-28	6 (3–10)	8 (4–12)	7 (4–11)	7 (4–11)
CRP (mg/dL)	0.8 (0.3–4.9)	1.7 (0.8–3.8)	1.4 (0.6–2.9)	1.4 (0.4–3.8)
PGA, mm*	43 (27–63)	62 (35–73)	58 (50–70)	52 (35–70)
DAS28-ESR*	5.3 (4.4–6.2)	5.7 (5.3–6.7)	5.9 (5.3–6.5)	5.7 (5.0–6.5)
DAS28-CRP	4.6 (3.6–5.6)	4.9 (4.5–5.7)	5.1 (4.7–5.8)	5.0 (4.3–5.7)
SDAI	23 (15–36)[b]	29 (25–44)[c]	25 (22–28)[d]	27 (19–40)[e]
CDAI*	19 (13–33)[b]	28 (23–41)[c]	22 (19–27)[d]	24 (18–37)[e]
MBDA score	62 (50–76)	65 (50–77)	64 (46–74)	64 (49–76)

CDAI clinical disease activity index, *CRP* C-reactive protein, *DAS28-CRP* 28-joint disease activity score with CRP, *DAS28-ESR* 28-joint disease activity score with erythrocyte sedimentation rate, *IQR* interquartile range, *MBDA* multi-biomarker disease activity, *MTX* methotrexate, *PGA* patient global assessment, *RF* rheumatoid factor, *RA* rheumatoid arthritis, *SDAI* simplified disease activity index, *SJC-28* swollen 28-joint count, *TJC-28* tender 28-joint count.
'*' Indicates variables that show statistical differences across the three TNF inhibitors ($p < 0.05$).
[a]For patients receiving concomitant MTX; [b]n = 35; [c]n = 30; [d]n = 22; [e]n = 87.

Results

Baseline characteristics

Baseline characteristics were typical of patients with long-standing active RA disease and were summarized in Table 1. The overall cohort ($N = 147$) was composed of 3 groups, with 49 patients for each TNF inhibitor (ADA, ETN, or IFX). In the overall cohort, 84% were female and 86% were rheumatoid factor-positive (RF+), with no statistically significant differences among the 3 TNF inhibitor groups. Likewise, there were no statistically significant differences in the median TJC-28, SJC-28, CRP, SDAI, DAS28-CRP and MBDA score among these 3 groups. Age, disease duration, concomitant use of MTX, PGA, DAS28-ESR and CDAI showed statistically significant differences among the treatment groups. Patients in the IFX group were significantly younger than those in the ADA and ETN groups (median age 55 years vs. 64 and 61 years, respectively). Patients in the ETN group had the longest disease duration (median 108 months vs. 48 and 47 months for ADA and IFX) and were less likely to have received concomitant MTX (61%) than those who received ADA (98%) or IFX (100%). Patients in the ADA group had the lowest median values for PGA and DAS28-ESR. Baseline median CDAI was significantly different among the 3 groups ($p < 0.05$), being lowest for the ADA group and highest for the ETN group.

Response to treatment

In the overall study cohort ($N = 147$), EULAR good response was achieved in 56% of the patients, and EULAR moderate response was achieved in an additional 35% of the patients. There was no significant difference in the distribution of patients by EULAR response category across the three TNF inhibitor groups. At 52 weeks, the median MBDA score was 34 (from 64 at baseline), and low disease activity (MBDA score < 30) was achieved in 37% of the patients. There was no statistically significant difference in the median MBDA scores among the three TNF inhibitor groups at each of the time points (Figure 1).

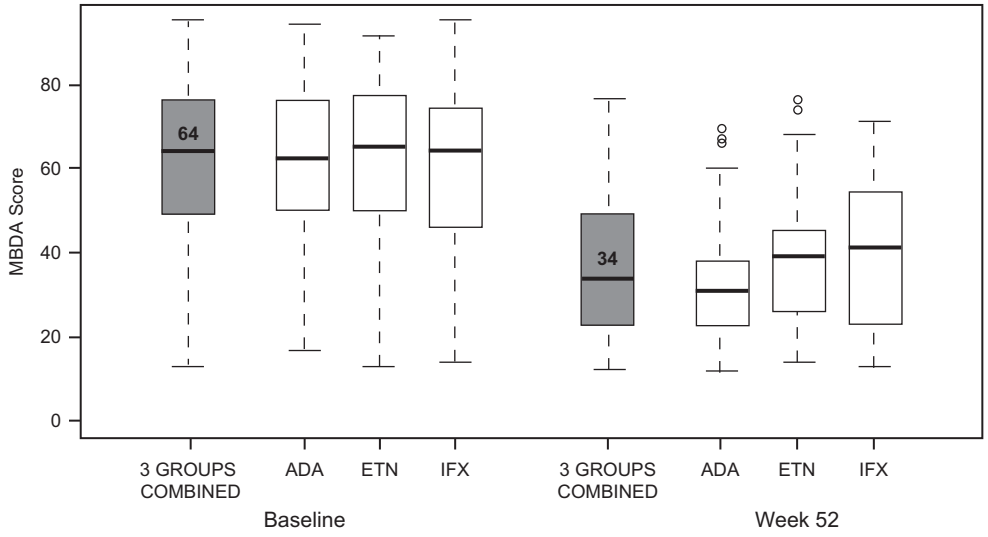

Figure 1. MBDA scores at baseline and after 52 weeks of treatment with TNF inhibitors ($N = 147$). Box and whisker plot of MBDA scores at baseline and 52 weeks after initiation of TNF inhibitor treatment (ADA, ETN, and IFX). Thick horizontal line: median value; box: interquartile range (IQR); whiskers: most extreme points within 1.5 times the IQR from the limits of the box. ADA: adalimumab; ETN: etanercept; IFX: infliximab; MBDA: multi-biomarker disease activity; TNF: tumor necrosis factor.

From baseline to 52 weeks, a significant median decrease in MBDA score (−42%) was observed. Significant median decreases were also observed with DAS28-ESR (−2.7 [−50%]) and DAS28-CRP (−2.6 [−55%]). Significant median decreases in SDAI (−21 [−87%]) and CDAI (−19 [−87%]) were also observed for the subset of patients who had available data ($N = 75$).

Relationship between changes in MBDA score and changes in composite clinical disease activity measures

ΔMBDA scores from baseline to 52 weeks significantly correlated with ΔDAS28-ESR ($r = 0.48$, 95% Confidence Interval (CI) 0.34–0.60) and ΔDAS28-CRP ($r = 0.46$, 95% CI 0.31–0.59). Across the three treatment groups, similar correlations were observed between ΔMBDA scores and ΔDAS28-ESR (ADA: 0.43, ETN: 0.55, IFX: 0.50) and also between ΔMBDA scores and ΔDAS28-CRP (ADA: 0.48, ETN: 0.47 and IFX: 0.44). In addition, ANCOVA showed no significant differences in the linear relationship between ΔMBDA scores and ΔDAS28-ESR (Figure 2a), in a comparison of the three TNF inhibitor groups ($p = 0.68$) or in pairwise comparisons of ADA vs. ETN ($p = 0.64$), ADA vs. IFX ($p = 0.67$), or ETN vs. IFX ($p = 0.38$). Likewise, ANCOVA showed that the linear relationship between ΔMBDA score and ΔDAS28-CRP (Figure 2b) were not significantly different across the three groups ($p = 0.59$) or in pairwise comparisons: ADA vs. ETN ($p = 0.92$), ADA vs. IFX ($p = 0.40$), or ETN vs. IFX ($p = 0.38$). Thus, the relationships between ΔMBDA scores and ΔDAS28-ESR or ΔDAS28-CRP appeared to be consistent across ADA, ETN and IFX. No significant correlations were observed between ΔMBDA scores from baseline to 52 weeks and ΔCDAI or ΔSDAI for the subset of 75 patients with available CDAI and SDAI scores (Electronic Supplementary Table 1 available online at: http//informahealthcare.com/doi/abs/10.3109/14397595.2014.958893).

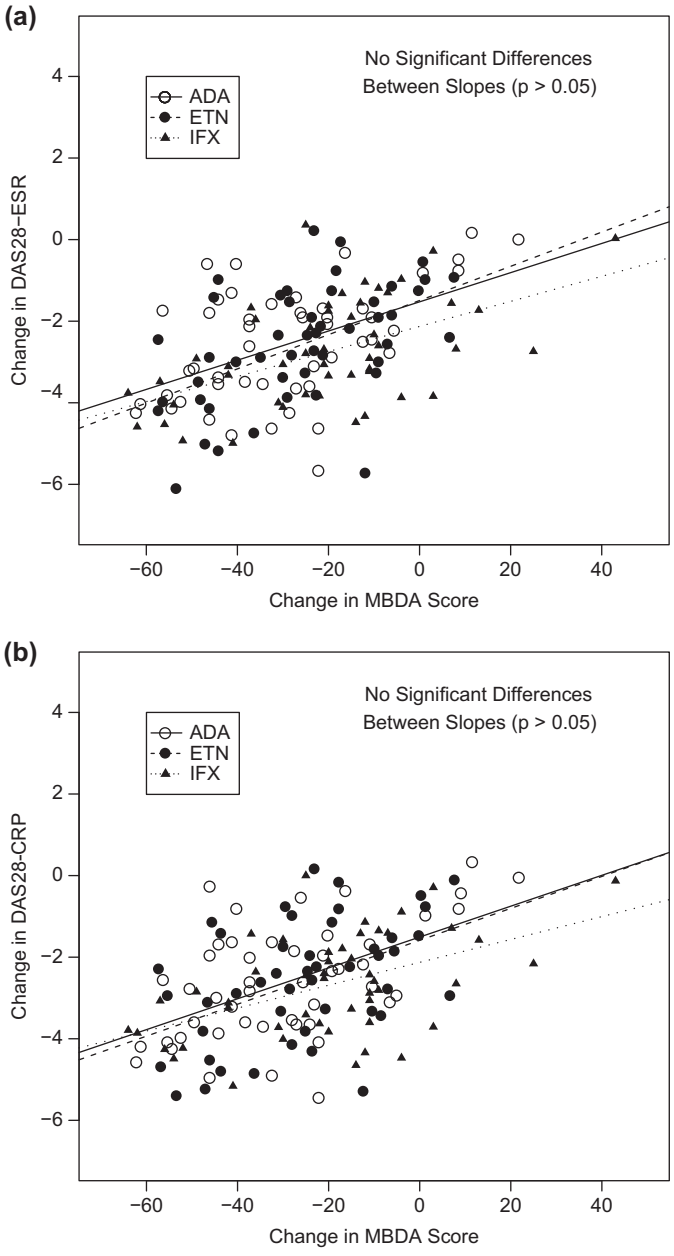

Figure 2. Scatterplot and regression lines for ΔDAS28-ESR (a) or ΔDAS28-CRP (b) versus ΔMBDA score from baseline to week 52, by TNF inhibitor. Each line was fitted by least square error separately for each group. ADA: adalimumab; DAS28-ESR: Disease Activity Score-28 with erythrocyte sedimentation rate; ETN: etanercept; IFX; infliximab; MBDA: Multi-biomarker disease activity; TNF: tumor necrosis factor.

Relationship between ΔMBDA score and EULAR response

At week 52, median changes in MBDA scores were –29, –21 and +2 for good, moderate and non-responders, respectively. Overall, EULAR good responders had significantly greater decreases from baseline in the MBDA score than EULAR moderate responders ($p = 0.007$), who in turn had significantly greater decreases in the MBDA score than EULAR non-responders ($p < 0.001$) (Figure 3). In the subgroup of 84 patients with data available at week 24, similar trends were observed for the decreases in MBDA score from baseline to week 24, stratified by the EULAR response at week 52 (Electronic Supplementary Figure 1 available online at: http//informahealthcare.com/doi/abs/10.3109/14397595.2014.958893). Furthermore, for this subgroup, the median decreases in MBDA score from baseline to week 24 were similar to the median decreases from baseline to week 52 (EULAR moderate responders: −16 vs. −21; EULAR good responders: −27 vs. −32), indicating, for responders, of the improvement observed in MBDA score at week 52 had been achieved by week 24.

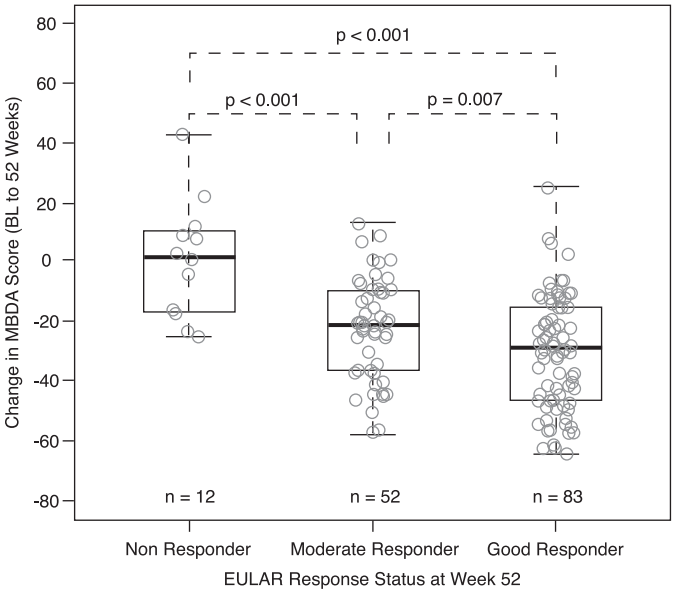

Figure 3. Changes (Δ) in MBDA score by EULAR response at week 52. Box and whisker plot of ΔMBDA score from baseline to 52 weeks after initiation of TNF inhibitor treatment in patients with no, moderate, and good treatment response at 52 weeks as defined by EULAR criteria. Statistical significance of the difference between the responder groups was assessed by Wilcoxon's rank-sum test. Thick horizontal line: median; box: interquartile range (IQR); whiskers: most extreme points within 1.5 times the IQR from the limits of the box. BL: baseline; EULAR: European League Against Rheumatism; IQR: interquartile range; MBDA: multi-biomarker disease activity; TNF: tumor necrosis factor.

Discussion

In this observational study, we assessed the relationship between changes in MBDA scores and changes in composite clinical disease activity measures and EULAR responses, in a cohort of Japanese patients with RA treated with three TNF inhibitors (ADA, ETN, IFX), in a routine clinical care setting. This study was designed to evaluate the performance of the MBDA score during TNF inhibitor therapy and determine its ability to consistently track disease activity in patient groups treated with different TNF inhibitors.

Patients had high disease activity at study entry with an overall median DAS28-ESR greater than 5.1 and median MBDA score greater than 44 in all three TNF inhibitor groups. A significant decrease in clinical disease activity and in MBDA scores was observed for all three groups following initiation of anti-TNF therapy. Low MBDA score (<30) was achieved in 37% of the patients at 52 weeks. The overall MBDA scores had similar distributions across the three treatment groups before and after treatment. It is important to note that the study was not designed as a head-to-head comparison of the TNF inhibitors and no comparison of treatment efficacy should be made.

Changes in MBDA scores from baseline to 52 weeks were significantly correlated with changes in DAS28-ESR and DAS28-CRP in the overall cohort of 147 patients. Changes in MBDA scores did not show significant correlation with changes in SDAI and CDAI for the subset with available data. This lack of correlation could be due at least in part to differences in how these indices measure disease activity. The MBDA score is an objective measure that evaluates the underlying biological processes associated with RA, while SDAI and CDAI rely heavily on subjective assessments such as TJC, SJC and PGA, and are a reflection of external signs and symptoms of the disease. Although similar clinical components are also used in the calculation of DAS28-ESR and DAS28-CRP, the fact that they are weighted less heavily in these scores than in SDAI and CDAI could explain the differences in the correlation results observed in this cohort. In view of these considerations, the MBDA score and clinically based measures may provide complementary information for assessing disease activity in patients with RA.

It is conceivable that, because the TNF inhibitors might differ in some aspects of their mechanisms of action, given that ETN is a receptor antagonist while ADA and IFX are anti-TNF antibodies, they might also differ in how they affect the relationship between the MBDA score and clinical measures of disease activity in particular. We found no significant treatment-related differences in the relationship between ΔMBDA score and ΔDAS28-ESR or ΔDAS28-CRP, indicating that the MBDA scores reported disease activity improvement in a consistent manner across these TNF inhibitors. These results suggest that, in routine clinical practice, the MBDA score can be interpreted in a similar manner during treatment with ADA, ETN and IFX.

A significant association was observed between an improvement in disease activity, as characterized by the ΔMBDA score and the EULAR response. Decreases in MBDA scores from baseline to 24 and 52 weeks were greater in EULAR good responders than in EULAR non-responders. This association is in agreement with the study showing that changes in the MBDA score were associated with changes in DAS28-CRP and ACR50 responses at 12 weeks for patients receiving MTX and/or anti-TNF therapy [17]. In that study, significant changes were detectable as early as 2 weeks after therapy initiation.

One limitation to consider when interpreting the results of the analyses is that the patient distribution was skewed toward good responders as the study aimed to assess the MBDA score in patients who maintained TNF inhibitor treatment for at least 1 year. The overall magnitude of decrease of MBDA score and the correlation between the changes of MBDA scores and the changes of clinical disease activity measures might differ in a population with a higher proportion of non-responders.

The findings from this study are based on single center observations and would need to be confirmed in larger independent cohorts. Additional studies that examine the MBDA score in the context of therapies with other modes of action, in particular those targeting MBDA component biomarkers, and studies in patients with comorbidities that might affect concentrations of acute phase proteins and markers of global inflammations, such as infections or malignancies, would further inform the clinical utility of the score. Lastly, analyses including radiographic outcome data could improve the understanding of how the disease activity measured by MBDA scores relates to clinical outcomes, especially when the MBDA score is discordant with DAS28.

In summary, the MBDA score reflected clinical disease activity and response to treatment with TNF inhibitors in patients with established RA. It showed similar behavior in patients treated with ADA, ETN, or IFX.

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Contributors

All authors on this article contributed to data analysis, interpretation, and writing or critical review of this manuscript. In addition, Dr. Hirata, Dr. Saito, Dr. Yamaoka, Prof. Tanaka and Dr. Cavet contributed to study design and execution.

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Conflict of interest

Yoshiya Tanaka, Prof., M.D., Ph.D., has received consulting fees, speaking fees, and/or honoraria from Mitsubishi-Tanabe, Eisai, Chugai, Abbott Japan, Astellas, Daiichi-Sankyo, AbbVie, Janssen, Pfizer, Takeda, AstraZeneca, Eli Lilly Japan, GlaxoSmithKline, Quintiles, MSD, Asahi-Kasei and has received research grants from Bristol-Myers, Mitsubishi-Tanabe, AbbVie, MSD, Chugai, Astellas, Daiichi-Sankyo.

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Wanying Li, Ph.D., Rebecca Bolce, MSN, and Nadine Defranoux, Ph.D., are employees of Crescendo Bioscience, Inc.

Guy Cavet, Ph.D. is a consultant to Crescendo Bioscience Inc.

Shintaro Hirata, M.D., Ph.D., and Kazuyoshi Saito, M.D., Ph.D., have no competing interests.

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Supplementary material available online

Electronic Supplementary Table 1 and Figure 1.