Improvement in matrix metalloproteinase-3 independently predicts low disease activity at 52 weeks in bio-switch rheumatoid arthritis patients treated with abatacept

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Abstract

Objective

To explore predictive factors including MMP-3 for achievement of low disease activity (LDA) at 52 weeks in bio-switch rheumatoid arthritis (RA) patients treated with abatacept, for whom obtaining a good clinical response can be difficult.

Methods

Participants were 423 consecutive patients with RA treated with abatacept who were observed for longer than 52 weeks and registered in the TBCR, a Japanese multicentre registry system. Multivariate logistic regression analysis was used to study factors that predict the achievement of LDA at 52 weeks in bio-naïve (n=234) and bio-switch (n=189) groups.

Results

ROC analysis revealed that MMP-3 improvement rates at 12 weeks in bio-switch patients had the highest AUC with a cut-off value of 20.0% for predicting LDA achievement at 52 weeks. Multivariate logistic regression analysis revealed that, in addition to DAS28-CRP at baseline, achieving 20% improvement in MMP-3 levels at 12 weeks was an independent predictive factor (adjusted OR: 4.277, p=0.003) in the bio-switch group, whereas DAS28 was the only predictor in the bio-naïve group. Patients who achieved 20% improvement in MMP-3 levels at 12 weeks had significantly higher achievement rates of LDA at 52 weeks compared to those who did not achieve 20% improvement in the bio-switch group (60.0 vs. 33.3%, p=0.001).

Conclusions

Our findings suggest that improvement in MMP-3 levels is key to predicting the clinical efficacy of abatacept. Closer attention paid not only to major clinical indices, but also changes in MMP-3 levels, could improve our ability to optimise clinical results when treating bio-switch patients.

Key words

rheumatoid arthritis, abatacept, matrix metalloproteinase 3, forecasting

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Introduction

Abatacept (ABA) is the first member of a new class of biological disease-modifying anti-rheumatic drugs (bDMARDs) for rheumatoid arthritis (RA) that inhibits T lymphocyte activation by binding to CD80/86, thereby modulating the CD80/86-CD28 interaction. ABA has been used in Japan since 2011 and some studies have demonstrated its clinical efficacy and safety in Japanese patients. In daily practice, it can be difficult to obtain an adequate response to ABA therapy in patients previously treated with bDMARDs (hereafter, bio-switch patients) (1). A Japanese post-marketing surveillance (PMS) study found that prior use of bDMARDs negatively affected the clinical response to ABA at 24 weeks (2). We also reported that no previous use of bDMARDs was an independent predictor for good clinical responses both at 24 weeks and 52 weeks (3, 4). Results from the nationwide Danish DANBIO registry indicated an unfavourably low drug retention rate of ABA in patients with RA treated in routine clinical practice, 97% of whom had a prior history of bDMARD use (5). Evidently, there is a high level of interest in defining as many predictive factors as possible for the clinical response to ABA in order to offer adequate treatment to bio-switch patients.

We previously reported that DAS28-CRP scores and concomitant steroid use predicted achievement of low disease activity (LDA) at 52 weeks (4). Other previous studies have identified several predictive factors for the clinical response to ABA other than prior DMARD history, including disease activity scores and seropositivity. The proportion of T follicular helper-like (Tfh-like) cells was higher in ACPA-positive patients and that among CD4+CD28+ cells was significantly reduced by ABA therapy (6, 7). A post-hoc analysis performed on the AGREE study demonstrated that the conversion of RF and ACPA to sero-negative status was associated with higher remission rate and lower radiographic progression (8, 9). Kubo *et al*. found that simplified disease activity index (SDAI) scores at baseline and rheumatoid factor (RF) titre were significantly associated with clinical disease activity index (CDAI) at week 52 (10). A Japanese PMS study demonstrated that functional disability, seropositivity for RF or anti-cyclic citrullinated peptide antibody (ACPA), and concomitant methotrexate (MTX) use in high disease activity patients predicted the achievement of clinical response at 24 weeks (2). The French ORA registry reported that DAS28-ESR scores and anti-cyclic citrullinated peptide (CCP) positivity predicted the achievement of EULAR response (11). However, no studies to date have described predictive factors for clinical outcomes of ABA in bio-switch RA patients. The identification of novel predictive factors is valuable in daily clinical practice, as achieving an adequate response in bio-switch patients is often difficult.

Matrix metalloproteinase-3 (MMP-3) is a proteolytic enzyme, also known as stromelysin-1, and thought to play a pivotal role in joint damage in RA. MMP-3 is involved in the degradation mechanism of articular cartilage in RA by cleaving extracellular matrix proteins; collagen type 2, 3, 4, 9, and 10, and proteoglycans. MMP-3 is locally produced by synovial fibroblasts and chondrocytes in the inflamed joint and released into blood (12, 13). Serum MMP-3 levels have been utilised as a valuable biomarker for assessing disease activity and predicting joint damage in RA patients (14-16). The multiple-biomarker disease activity (MBDA) comprises 12 serum biomarkers including MMP-3 and was shown to reflect disease activity and predict joint destruction (17, 18). We have found that percent improvement in MMP-3 levels was a significant predictor for clinical remission in RA patients treated with adalimumab (19). Interestingly, the absolute value of MMP-3 was not associated with clinical outcomes of adalimumab.

In this study, we explored several potential predictive factors for achieving an adequate response to ABA among bio-switch patients using data from a Japanese multicentre registry system. Our main focus was to identify whether or not percent improvement in MMP-3 levels, as well as other clinical charac-

teristics, could independently predict the achievement of LDA at 52 weeks.

Materials and methods

Participants

All eligible patients were registered in and followed by the Tsurumai Biologics Communication Registry (TBCR). The TBCR is a registry of patients with RA starting treatment with biologics in 2008 that was developed to analyse the long-term prognosis of patients undergoing treatment with biologics in clinical practice (3, 20). Data were collected prospectively beginning in 2008, as well as retrospectively for patients who had been treated with biologics through 2008. All 2,827 patients registered in the TBCR as of April 2015 met the 1987 American College of Rheumatology (ACR) or the 2010 ACR/ European League Against Rheumatism (EULAR) classification criteria for RA (21). Information on medication history was collected at clinic visits to TBCR-affiliated institutions. Registry data are updated once per year and include information on drug continuation, reasons for discontinuation (*e.g.* insufficient efficacy), and adverse events. Patient anonymity was maintained during data collection, and security of personal information was strictly controlled. This study was approved by the Nagoya University Graduate School of Medicine Ethics Committee (approval no.: 2011-1164). Written informed consent was obtained from all participants of this study.

The present study included 423 consecutive patients treated with intravenous (IV) ABA and prospectively observed for longer than 52 weeks at TBCR-affiliated institutions. Since ABA has been commercially available for RA treatment since 2011, data in this study were all prospectively collected. Patients received IV ABA infusions three times with 2-week intervals between infusions, and thereafter at 4-week intervals, according to drug labels and the Japan College of Rheumatology guidelines for treatment. Patients received a fixed dose of ABA at roughly 10 mg/kg body weight; patients weighing <60kg received 500 mg of ABA, those weighing 60–100 kg received 750 mg, and those weighing >100 kg received 1000 mg.

Data collection

The following demographic data were recorded at the initiation of treatment (baseline, week 0): age, sex, disease duration, joint damage (Steinbrocker stage), daily dysfunction (Steinbrocker class), rheumatoid factor (RF) positivity (≥20 IU/ml), history and number of previous bDMARDs, and concomitant treatment (methotrexate [MTX] and prednisolone [PSL]). The following disease parameters were recorded at baseline and after 4, 12, 24, and 52 weeks of treatment: tender joint count (TJC) and swollen joint count (SJC) on 28 joints, patient (PtGA) and physician (PhGA) global assessment of disease activity, modified health assessment questionnaire (mHAQ) score (22, 23), serum c-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), and matrix metalloproteinase-3 (MMP-3) levels. Disease activity was evaluated at baseline and 4, 12, 24, and 52 weeks using the 28-joint disease activity score with CRP (DAS28-CRP), which includes data from the above-mentioned disease parameters. The EULAR response was evaluated at 4, 12, 24, and 52 weeks (24). Data from bio-naïve patients were analysed separately from those of bio-switch patients.

Disease activity and EULAR response

Disease activity was categorised as follows: DAS28 remission (DAS28-CRP <2.6), low disease activity (LDA; 2.6≤ DAS28-CRP <3.2), moderate disease activity (MDA; 3.2≤ DAS28-CRP ≤5.2), and high disease activity (HDA; DAS28-CRP>5.1). Disease activity was evaluated at baseline and 24 weeks after treatment. European League Against Rheumatism (EULAR) response was evaluated at 24 weeks (24).

Statistical analysis

Demographic and disease characteristics are reported using descriptive statistics. All results are expressed as mean ± standard deviation (SD) or percentage (%). Student's *t* test was used for 2-group comparisons, and the chi-square test for categorical variables. The last observation carried forward (LOCF) method was used in each analysis.

Receiver operating characteristic (ROC) curves were constructed to determine the best cut-off point for percent improvement in MMP-3 levels at 12 weeks, and the area under the ROC curve (AUC) was calculated as a measure of the overall discriminative ability of percent improvement in MMP-3 levels. The cut-off point was identified as that closest to the (0, 1) point and taken to be the cut-off point that best differentiated between patients with and without achievement of LDA at 52 weeks.

Multivariate analysis (logistic regression) was performed to identify factors that predict the achievement of LDA at 52 weeks. We assessed age, sex, RF positivity, concomitant MTX, concomitant PSL, DAS28-CRP at baseline, mHAQ score at baseline, and 20% improvement in MMP-3 levels. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated after adjusting for age and gender.

All statistical tests were two-tailed, with significance defined as $p<0.05$. All analyses were performed with SPSS v. 22 software (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

Baseline characteristics of both groups (n=234 in bio-naïve; n=189 in bio-switch) are shown in Table I. Significant group-dependent differences were observed for age, sex, Steinbrocker stage/class, and SJC/TJC. Mean number of previous biologics in the bio-switch group was 1.6. In total, 112 patients had only one previous biologic treatment (used ABA as second biologic), 54 patients had two, 17 patients had three, 4 patients had four, and 2 patients had five.

Comparisons of scores and categorical distribution of DAS28-CRP

Mean DAS28-CRP score significantly decreased from baseline to 52 weeks in each group (bio-naïve: 4.26±1.24 to 2.79±1.26, $p<0.001$; bio-switch: 4.47±1.44 to 3.39±1.40, $p<0.001$) (Fig. 1A). Mean DAS28-CRP scores in the bio-switch group were significantly higher than those in the bio-naïve group at 4, 12, 24, and 52 weeks.

Table I. Baseline characteristics.

Variables n	Bio-naïve 237	Bio-switch 189	*p*-value
Age (year)	66.3 ± 11.6	62.9 ± 11.8	***0.004***
Gender (% female)	75.6	84.1	***0.032***
Disease duration (year)	12.0 ± 17.9	13.7 ± 12.8	0.305
Stage 1-2 (%)	43.9	22.6	***<0.001***
Class 1-2 (%)	60.5	48.9	***0.018***
RF positive (%)	72.9	80.2	0.161
No. previous bDMARDs	-	1.6 ± 0.8	-
MTX use (%)	49.6	46	0.469
MTX dose (mg/week)[a]	7.6 ± 3.1	7.6 ± 2.4	0.958
Oral PSL use (%)	48.9	51.9	0.543
Oral PSL dose (mg/day)[a]	4.7 ± 2.8	4.5 ± 2.6	0.672
DAS28-CRP	4.22 ± 1.27	4.46 ± 1.45	0.075
SJC, 0-28	4.2 ± 4.1	5.5 ± 5.9	***0.016***
TJC, 0-28	6.1 ± 6.2	7.8 ± 7.0	***0.017***
CRP (mg/dL)	1.9 ± 2.3	2.2 ± 2.8	0.295
PtGA 0-100 mm	51.8 ± 27.2	55.3 ± 27.2	0.211
ESR (mm/h)	54.9 ± 33.5	51.2 ± 33.2	0.290
PhGA 0-100 mm	44.0 ± 21.6	48.6 ± 23.9	0.059
MMP-3 (ng/mL)	237.9 ± 484.8	229.8 ± 269.3	0.850
mHAQ	0.7 ± 0.7	0.8 ± 0.7	0.271

Data are presented as mean ± standard deviation unless indicated otherwise.
Stage: Steinbrocker stage; Class: Steinbrocker class; RF: rheumatoid factor; bDMARDs: biological disease-modifying anti-rheumatic drugs; MTX: methotrexate; PSL: prednisolone; DAS28: Disease Activity Score in 28 joints; SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; PtGA: patient global assessment; ESR: erythrocyte sedimentation rate; PhGA: physician global assessment; MMP-3: matrix metalloproteinase-3; mHAQ: modified health assessment questionnaire.
[a] Mean among patients receiving the drug, ***Bold italics*** indicate statistical significance ($p<0.05$).

Figure 1B shows the DAS28-CRP categorical distribution by disease activity status. Proportions of patients who achieved LDA or remission increased significantly from baseline to 52 weeks for the bio-naïve (20.8 to 64.5%, $p<0.001$) and bio-switch (20.3 to 46.7%, $p<0.001$) groups. Achievement rates of LDA or remission were significantly lower in the bio-switch group compared to those in the bio-switch group at 12, 24, and 52 weeks ($p<0.001$).

ROC curves for percent improvement in MMP-3 levels

First, we examined the ROC curves for MMP-3 levels at baseline, 4 weeks, and 12 weeks for achievement of LDA at 52 weeks. However, the AUCs were low both in the bio-naïve (0.533, 0.590, and 0.617, respectively) and bio-switch (0.495, 0.525, and 0.583, respectively) groups.

ROC curves for percent change in MMP-3 levels from baseline at 4 weeks and 12 weeks for achievement of LDA at 52 weeks are shown in Figure 2. In the bio-naïve group, the AUC was low both at 4 (0.595) and 12 weeks (0.586). In the bio-switch group, the AUC at 12 weeks (0.642) was higher than that at 4 weeks (0.551) (Fig. 2). The cut-off value in the bio-switch group at 12 weeks was 20.0%. Since the main purpose of this study was to explore potential predictors of LDA at 52 weeks in the bio-switch group, we used '20% improvement in MMP-3 levels at 12 weeks' as a cut-off index for subsequent analyses.

Factors predicting achievement of LDA at 52 weeks

Multivariate logistic regression to identify predictors of LDA achievement at 52 weeks in the bio-naïve group was performed separately from that in the bio-switch group. We selected the following variables for analysis: age, sex, RF positivity, concomitant MTX, concomitant PSL, DAS28-CRP score at baseline, mHAQ score at baseline, and 20% improvement in MMP-3 levels at 12 weeks (Table II).

Multivariate logistic regression showed that only DAS28-CRP score at baseline was independently associated with achievement of LDA at 52 weeks in the bio-naïve group. In the bio-switch

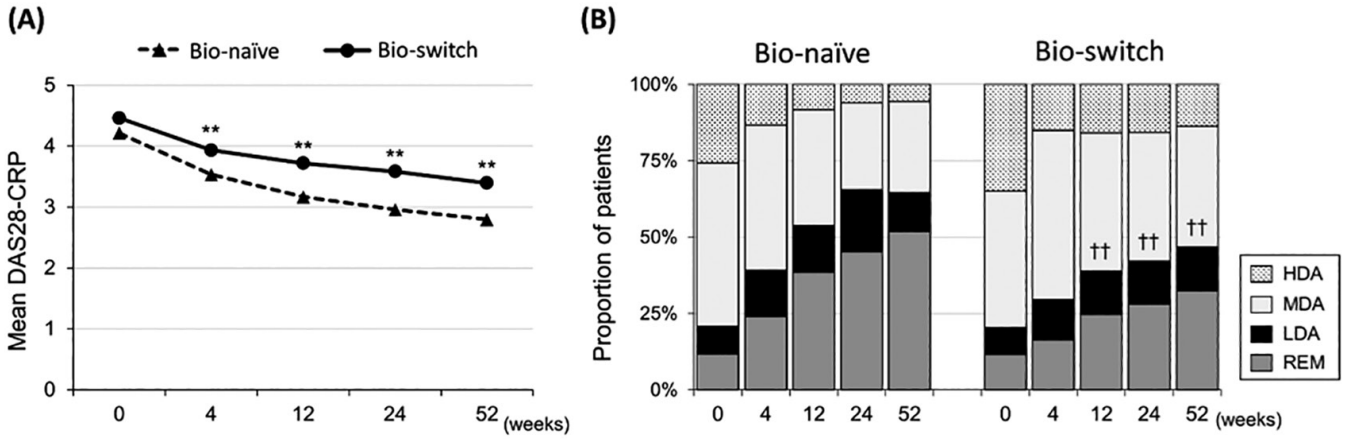
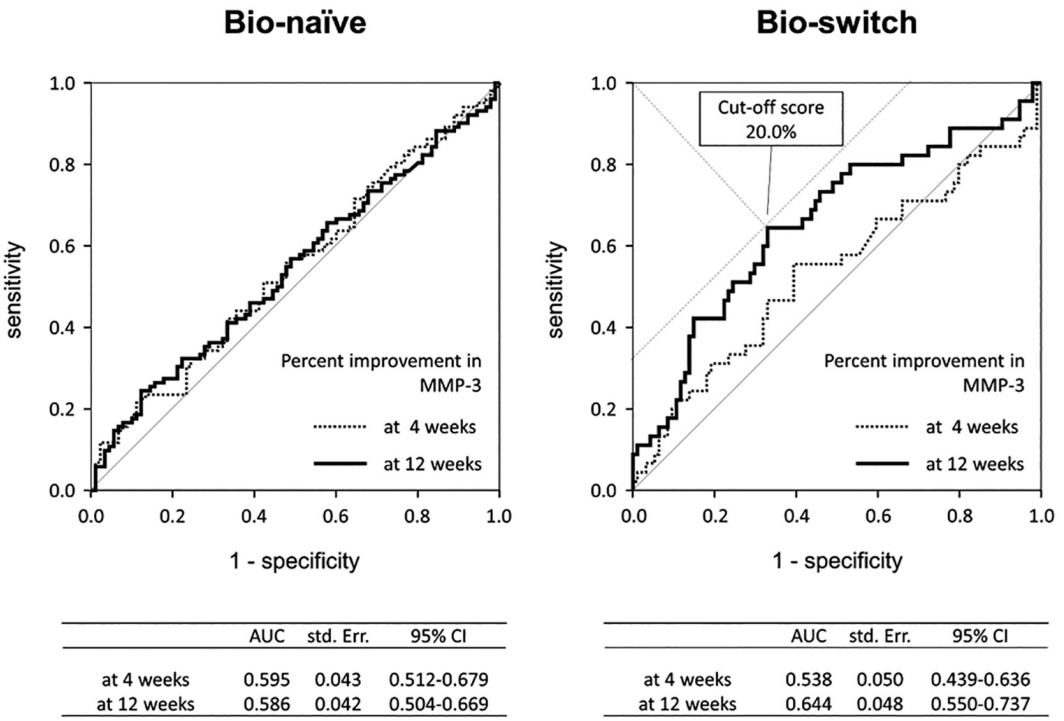


Fig. 1. Comparison of disease activity in bio-naïve and bio-switch groups.
A: Mean disease activity score based on 28 joints (DAS28-CRP). **B**: Categorical distribution of DAS28-CRP. HDA: high disease activity; MDA: moderate disease activity; LDA: low disease activity; REM: remission.
$^{**}p<0.01$ *vs*. bio-naïve group at each time point. $^{††}p<0.01$, comparing LDA achievement rate *vs*. bio-naïve group at each time point.



	AUC	std. Err.	95% CI
at 4 weeks	0.595	0.043	0.512-0.679
at 12 weeks	0.586	0.042	0.504-0.669

	AUC	std. Err.	95% CI
at 4 weeks	0.538	0.050	0.439-0.636
at 12 weeks	0.644	0.048	0.550-0.737

Fig. 2. Prognostic significance of percent improvement in MMP-3 levels at 4 and 12 weeks for predicting low disease activity at 52 weeks.
Receiver operating characteristic (ROC) curves for percent improvement in MMP-3 levels at each time point for predicting the achievement of low disease activity (LDA) at 52 weeks after starting abatacept treatment.
The table displays the area under the ROC curve (AUC), standard error (SE), and 95% CI for each time point.

group, in addition to DAS28-CRP score, 20% improvement in MMP-3 levels at 12 weeks was an independent predictor for achievement of LDA at 52 weeks (Table II).

Change in DAS28-CRP score and LDA achievement rate at 52 weeks is dependent on improvement in MMP-3 levels

We examined changes in DAS28-CRP scores and achievement rates of LDA in the bio-naïve and bio-switch groups (Fig. 3). In the bio-naïve group, patients with 20% improvement in MMP-3 levels at 12 weeks had significantly lower DAS28-CRP scores and higher achievement rates of LDA at 12 and 24 weeks compared to those without 20% improvement in MMP-3 levels. However, there was no significant difference in both DAS28-CRP score and LDA achievement rate at 52 weeks. On the other hand, there were significant differences in DAS28-CRP scores and LDA achievement rates between 4 to 52 weeks in the bio-switch group between those with and without 20% improvement in MMP-3 levels at 12 weeks. Additionally, among those who achieved 20% improvement in MMP-3 levels at 12 weeks, the bio-switch group had DAS28-CRP scores at 52 weeks (2.98±1.25 *vs*. 2.71±1.06, p=0.128) and LDA achievement rates at 52 weeks (60.0 *vs*. 68.9%, p=0.224) that were similar to those in the bio-naïve group, while the bio-switch group had significantly higher DAS28-CRP scores at 12 weeks (3.46±1.34 *vs*. 2.96±1.16, p=0.009) and lower LDA achievement rates at 12 weeks (61.7 *vs*. 47.7%, p=0.067) and 24 weeks (71.4 *vs*. 58.5%, p=0.074) (Fig. 3).

Table II. Factors associated with achievement of low disease activity at 52 weeks.

	Bio-naïve		Bio-switch	
Variables	Adjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age	0.998 (0.962-1.035)	0.926	0.990 (0.951-1.030)	0.627
Male (*vs*. female)	0.672 (0.289-1.566)	0.357	0.954 (0.266-3.418)	0.943
RF positive	2.117 (0.912-4.913)	0.081	0.427 (0.127-1.430)	0.167
Concomitant MTX	1.628 (0.764-3.468)	0.207	1.310 (0.522-3.289)	0.565
Concomitant PSL	0.680 (0.320-1.442)	0.314	0.580 (0.230-1.465)	0.249
DAS28-CRP at baseline	0.590 (0.413-0.844)	***0.004***	0.646 (0.449-0.930)	***0.019***
mHAQ score at baseline	0.672 (0.363-1.246)	0.207	0.588 (0.267-1.291)	0.186
20% improvement in MMP-3	1.884 (0.885-4.010)	0.100	4.277 (1.658-11.028)	***0.003***

Multivariate logistic regression analysis. RF: rheumatoid factor; MTX: methotrexate; PSL: prednisolone; mHAQ: modified health associated questionnaire; OR: odds ratio.
Bold italics indicate statistical significance (p<0.05).

Discussion

We found that percent improvement in MMP-3 levels independently predicted the achievement of LDA at 1 year in bio-switch patients treated with ABA, using 20.0% as a cut-off value for highest predictability at 12 weeks. The important finding of this study was that, for bio-switch patients with 20% improvement in MMP-3 levels at 12 weeks, ABA efficacy at 52 weeks was similar to that in bio-naïve patients. Achievement of 20% improvement in MMP-3 levels at 12 weeks would warrant continuation of ABA treatment in bio-switch patients, even if the clinical response remains insufficient.

Recently, Matsubara *et al*. reported the results of a Japanese phase IV clinical trial of ABA in RA patients with an insufficient response to MTX (25). ABA in combination with MTX demon-

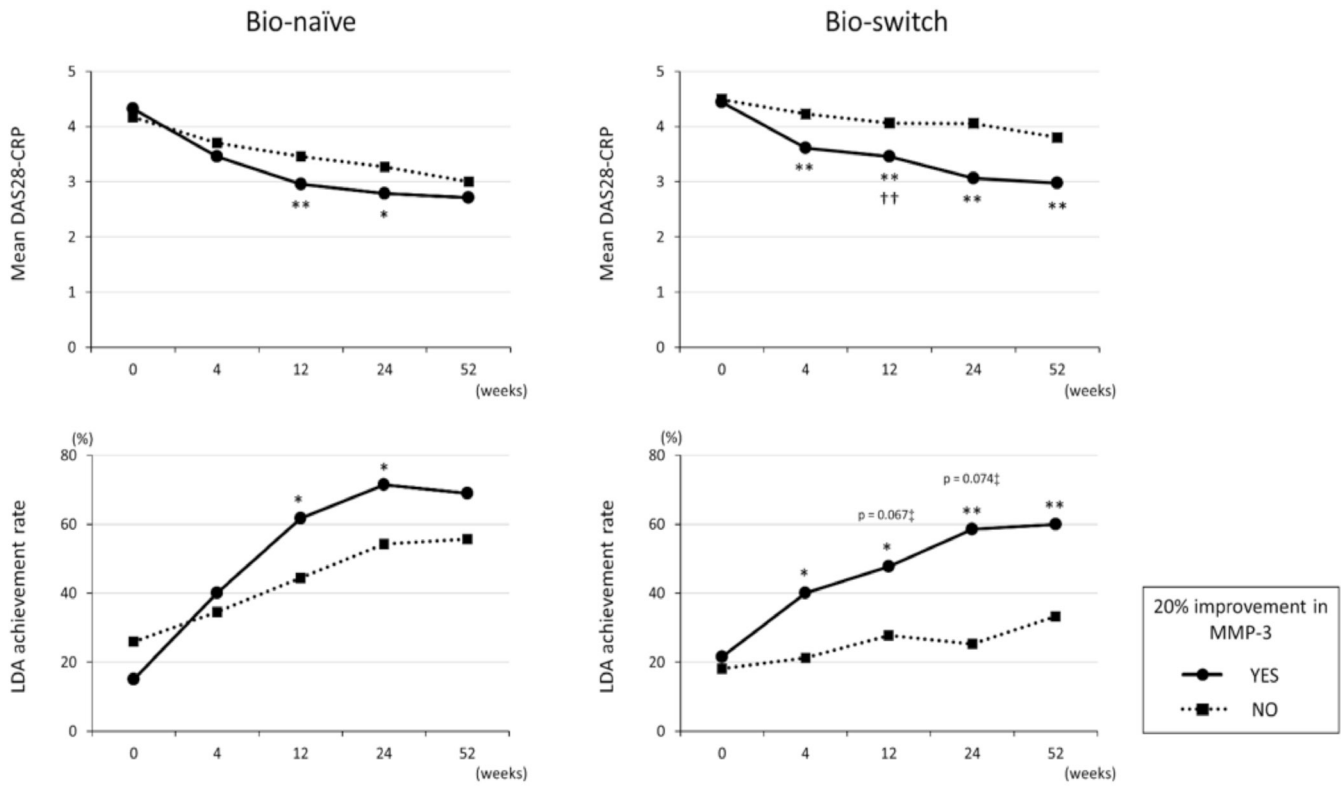


Fig. 3. Comparisons of DAS28-CRP score (upper row) and achievement of low disease activity (LDA) (upper row) between patients with and without 20% improvement in MMP-3 levels in bio-naïve and bio-switch groups.
*p<0.05, **p<0.01 *vs*. no 20% improvement in MMP-3 levels at 12 weeks. ††p<0.01, *vs*. bio-naïve group. ‡*vs*. bio-naïve group.

strated relatively high clinical efficacy (75.4% of ACR 20 response and 61.1% of DAS28-CRP remission) in bio-naïve patients. However, a good portion of patients treated with ABA in the 'real world' have been previously treated with biologics. In a Japanese PMS study, 70.2% of patients were classified as bio-switch patients and were less responsive to ABA treatment than bio-naïve patients (2). Others have also described the lower efficacy of ABA in bio-switch patients (4, 5). Indeed, the bio-switch group demonstrated significantly lower clinical efficacy of ABA in this study. Thus, in daily clinical practice, it is important to identify specific predictive factors that will likely lead to a good clinical response in bio-switch patients so that appropriate treatments can be provided to these patients. We found that 20% improvement in MMP-3 levels, as well as DAS28-CRP scores at baseline, were both independent predictive factors of LDA achievement at 52 weeks in bio-switch patients. This finding should assist rheumatologists as they work to offer appropriate treatment strategies to 'real world' RA patients.

Rather than using a simple change in MMP-3 levels from baseline (ΔMMP-3) or absolute values at each time point, the present study used percent change. One reason for this was that standard MMP-3 levels differed between men (36.9–121.0 ng/ml) and women (17.3–59.7 ng/ml). Additionally, steroid use and renal dysfunction are known to increase serum levels of MMP-3 independently of RA disease activity (26). Thus, it would be difficult to use ΔMMP-3 levels or absolute values of MMP-3 as common predictors when working with heterogeneous RA patient groups comprising both sexes, those with variable renal function, and those with and without steroid use. Indeed, we were unable to obtain good predictability (AUC) and reasonable cut-off values when using ΔMMP-3 levels and absolute values of MMP-3 to assess LDA achievement in the ROC curve analysis.

In bio-naïve patients, we did not find percent change in MMP-3 levels to be a significant predictor for LDA. There is no clear explanation for this group-dependent difference. However, since the clinical efficacy of ABA is markedly better overall in bio-naïve patients, it is possible that the relatively uniform clinical response may obscure predictors other than baseline disease activity.

This study has several limitations. First, we did not have data regarding concomitantly used conventional synthetic (cs) DMARDs other than MTX, such as salazosulphapyridine, bucillamine, and iguratimod. These drugs could have affected the clinical efficacy and retention rates of ABA. Second, sequential radiographic data were not available. Given the importance of joint protective effects in demonstrating clinical efficacy, evaluating radiographic changes in patients treated with ABA will be necessary in the future. Finally, our findings were all based on the use of IV ABA. However, the use of a new subcutaneous formulation is now widespread, and further studies will be needed to determine whether our results apply to subcutaneous ABA as well.

Conclusions

Our results suggest that improvement in MMP-3 levels at 12 weeks is key to predicting the clinical efficacy of ABA at 1 year. It will be important to pay closer attention not only to major clinical indices such as DAS28, but also to changes in MMP-3 levels, in order to optimise clinical outcomes when treating bio-switch patients with ABA.

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