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【 ORIGINAL ARTICLE 】

An Analysis of the Biological Disease-modifying Antirheumatic Drug-free Condition of Adalimumab-treated Rheumatoid Arthritis Patients

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Abstract:

Objectives The present study was performed with the aim of analyzing the biological disease-modifying antirheumatic drug (bDMARD)-free (Bio-free) condition of adalimumab (ADA)-treated rheumatoid arthritis (RA) patients in a real-world setting.

Methods ADA was used in the treatment of 130 (male, n=21; female, n=109 females) RA patients. Among them, 26 patients (20.0%) discontinued ADA due to a good response. We analyzed 20 patients who were followed up for more than 6 months after the discontinuation of ADA. The Disease Activity Score 28 based on C-reactive protein (DAS28-CRP) and modified health assessment questionnaires (mHAQs) were evaluated.

Results The mean age of the patients was 53.4±11.1 years. The mean disease duration was 4.5±4.3 years. Sixteen patients were bDMARD-naïve, while 4 switched from bDMARDs to ADA. At 6 months after the discontinuation ADA, 19 patients had achieved a clinical remission, and 1 had achieved a low disease activity. The Bio-free period was 26.4±15.5 months. The dose of prednisolone was significantly reduced from baseline (3.45±3.17 mg/day) at 6 months after the discontinuation of ADA (2.63±2.78 mg/day). The dose of methotrexate was unchanged. The number of conventional synthetic DMARDs (csDMARDs) was significantly increased (0.8±0.6 to 1.4±1.06). The mHAQ values were significantly ameliorated by ADA and remained good in patients with a Bio-free condition. A multivariate analysis showed that the dose of methotrexate (MTX) was an important factor for achieving a Bio-free condition.

Conclusion A sustainable Bio-free condition in a real clinical setting can be achieved and may be a suitable way of reducing medical costs. The dose of MTX and the additional administration of csDMARDs is therefore thought to be important for ensuring a good outcome in these patients.

Key words: rheumatoid arthritis, adalimumab, methotrexate, conventional synthetic disease-modifying antirheumatic drugs, biologics free condition

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Introduction

Adalimumab (ADA) is a fully human anti-tumor necrosis factor (TNF) α monoclonal antibody that is classified as a biological disease-modifying antirheumatic drug (bDMARD). The efficacy of ADA in the treatment of rheumatoid arthritis (RA) has been demonstrated, and the efficacy of ADA in combination with methotrexate (MTX) was documented in the PREMIER Study (1, 2). Burmester et al. and our own study group have shown that the efficacy of ADA depends on the dose of MTX (3, 4). It has been re-

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ported that clinical remission (CR), can be maintained while discontinuing ADA (entering a bDMARD-free or Bio-free condition) (5-9). However, the ultimate outcome of patients in a Bio-free condition is not necessarily good (10).

We herein report the actual status of patients in a Bio-free condition in a real-world setting and discuss the possible importance of the dose of MTX and the use of conventional synthetic DMARDs (csDMARDs).

Materials and Methods

Patients and ADA therapy

The study population included 130 patients (male, n=21; female, n=109) who had been prescribed ADA (40 mg, subcutaneously, every other week) between July 2008 and February 2016. The study was performed at the following locations: Niigata Rheumatic Center (n=117), Niigata Prefectural Kamo Hospital (n=5), and Ishii Clinic (private clinic, n=8). The participants received ADA therapy in accordance with the Guidelines for Anti-TNF Therapy in Rheumatoid Arthritis proposed by the Japan College of Rheumatology (JCR) (11).

The JCR criteria are similar to the European League Against Rheumatism (EULAR) criteria; thus, this initiative is also relevant to populations in other countries. Concomitant treatment with MTX, csDMARDs other than MTX, and/or steroids was prescribed at the discretion of the attending physicians. The doses of concomitant drugs were adjusted according to the standard medical practice for controlling disease activity. The tender joint count (TJC) and swollen joint count (SJC) of 28 joints were used as TJC and SJC.

Written consent was not obtained, but the publication of the results was approved by each ethics committee (Niigata Rheumatic Center: NO. 2018-004, Niigata Prefectural Kamo Hospital: NO. 2018.1, and Ishii Clinic: NO. 2018.1).

Decision to discontinue ADA

The decision to discontinue ADA was made by the patients and their physicians. Precise criteria were not established, but when a CR was maintained for more than two years, we proposed the discontinuation of ADA. If a patient indicated that they wanted to be bDMARD (Bio)-free before reaching the two-year remission point due to financial reasons, then ADA was discontinued. We explained to the patients that while the outcomes of a Bio-free condition have been reported to be quite good, they are not as good as the outcomes that are obtained when continuing bDMARDs (7-9). Since the early introduction of ADA was approved in Japan in 2012 (simultaneous use with csDMARDs), we have recently been explaining the possibility of entering a Bio-free condition to patients with high disease activity (HDA) when considering the introduction of ADA.

Addition of csDMARDs other than MTX

When the patients could not achieve CR before the Bio-free period, csDMARDs were added. When patients agreed to add csDMARDs at the discontinuation of ADA, one csDMARD was added. csDMARDs were added when patients experienced a relapse after the discontinuation of ADA-if they indicated that they did not wish to re-start ADA

Clinical efficacy and the treatment retention rate

The disease activity of the patients was assessed using the Disease Activity Score 28 based on C-reactive protein (DAS 28-CRP) (12) because the erythrocyte sedimentation rate (ESR) could not be measured at the Ishii Clinic. The disease activity measured by DAS28-CRP was defined as follows: CR, <2.3; low disease activity (LDA), 2.3 to 2.7; moderate disease activity (MDA), 2.7 to 4.1; and HDA, >4.1 (13).

The severity of the functional disorder was assessed using the modified health assessment questionnaire (mHAQ) (14).

We discontinued ADA in 26 patients (20.0%) who showed a good response. Twenty-five patients achieved a CR, and one indicated that they wanted to be in a Bio-free condition with LDA. We analyzed the 20 patients who could be followed up for more than 6 months (bDMARDs naïve, n=16; switched from bDMARD, n=4). The Bio-switch group included one patient who maintained a CR with etanercept (ETN), but who wanted to be in a Bio-free condition with ADA, a patient with secondary failure with ETN, and two patients with secondary failure with infliximab (IFX).

Statistical analyses

Comparisons between two independent groups were performed using the Mann-Whitney U test. Comparisons between paired samples were performed using the Wilcoxon signed-rank test. Fisher's exact test was used to analyze associations between categorical variables. Statistically significant variables with $p<0.05$ in the patient background analysis, age and gender were then entered into a logistic regression model. Because of the limited number of bio-free patients, TJCs were represented by DAS28-CRP. p values of < 0.05 were considered to indicate statistical significance. All of the statistical analyses were performed using the IBM SPSS Statistics Package (Ver. 22.0, IBM, Armonk, USA).

Results

The characteristics of the Bio-free patients (n=20 and 26) and non-Bio-free patients (n=104).

Some patients in the non-Bio-free group might be able to achieve a Bio-free condition in the future. Table 1 summarizes the demographic and clinical characteristics of the participants at baseline. When we evaluated the Bio-free patients who were followed up for more than 6 months after the discontinuation of ADA (n=20), the dose of MTX in the

Table 1. Background of the Patients.

	All		Bio-free group (n=20)		Bio-free group (n=26)		Non Bio-free group (n=104)		20 vs. 104	26 vs. 104
	n		n		n		n		p value	p value
Age	130	53.1±13.2	20	53.4±11.1	26	51.2±11.9	104	53.6±13.5	0.973	0.422
Sex (male, female)	130	(21, 109)	20	(6, 14)	26	(6, 20)	104	(15, 89)	0.106 *	0.574 *
% of female	130	83.8%	20	76.9%	26	76.9%	104	85.6%		
Disease duration (years)	130	7.4±8.9	20	4.5±4.3	26	3.8±4.0	104	8.4±9.5	0.28	0.0601
MTX dose (mg/week)	120	9.35±2.72	20	10.7±2.72	26	10.1±2.9	94	9.1±2.76	0.0259	0.0892
MTX usage	130	92.3%	20	100%	26	100%	94	90.4%	0.363 *	0.21 *
PSL dose (mg/week)	84	4.92±2.31	14	4.93+2.66	16	3.2±3.3	68	4.9±2.2	0.782	0.920
PSL usage	130	64.6%	14	70%	26	61.5%	68	65.4%	0.8*	0.819*
Height (cm)	130	157.1±8.1	20	161.5±6.98	26	161.4±6.6	104	156.1±8.2	0.00657	0.0019
Weight (kg)	130	55.0±10.4	20	59.2±11.9	26	58.3±11.2	104	54.3±10.1	0.0554	0.0604
BMI (kg/m^2)	130	22.3±3.6	20	22.6±3.6	26	22.2±3.4	104	22.3±3.6	0.755	0.993
RF	130	129.2±178.7	20	106.7±166.9	26	119.2±170.5	104	131.7±180.6	0.313	0.344
ACPA (U/mL)	129	181±252	20	310±463	26	288±425	103	154±181	0.225	0.166
TJC	130	4.81±4.58	20	3.5±5.26	26	4.0±5.4	104	5.0±4.3	0.00741	0.0158
SJC	130	4.87±4.49	20	5.05±4.97	26	4.3±4.8	104	5.2±4.4	0.689	0.214
Pt.VAS (mm)	130	43.4±22.6	20	36.2±20.9	26	36.9±21.3	104	45.1±22.7	0.116	0.125
CRP (mg/dL)	130	2.23±2.5	20	1.38±2.09	26	1.1±1.9	104	1.9±2.6	0.274	0.0529
DAS28-CRP	130	3.95+1.24	20	3.5±1.3	26	3.4±1.3	104	4.1±1.2	0.0254	0.00976
mHAQ	87	0.531±0.483	15	0.313±0.436	21	0.386±0.451	66	0.577±0.48	0.0492	0.109

Statistical analyses were performed using the Mann-Whitney U test or Fisher's exact test *.

MTX: methotrexate, PSL: prednisolone, BMI: body mass index, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, TJC: tender joint counts, SJC: swollen joint counts, Pt VAS: patient's visual analogue scale, CRP: C-reactive protein, DAS: disease activity score, mHAQ: modified Health Assessment Questionnaire

Table 2. Predictive Factors for Bio-free.

	Odds ratio	95% CI	p value
Age (per year)	1.04	0.956 - 1.11	0.324
Male gender	0.266	0.0193 - 3.66	0.322
MTX dose (per mg/week)	1.26	1.00 - 1.58	0.0488
Height (per cm)	1.04	0.994 - 1.29	0.0617
DAS28-CRP (per unit)	0.864	0.448 - 1.67	0.663
mHAQ (per unit)	0.314	0.0533 - 1.85	0.201

CI: confidence interval, MTX: methotrexate, CRP: C-reactive protein, DAS: disease activity score, mHAQ: modified Health Assessment Questionnaire

Bio-free group was significantly higher than that in the non-Bio-free group (10.7±2.72 vs. 9.1±2.76 mg/week). The patients in the Bio-free group were significantly taller than those in the non-Bio-free group (161.5±6.98 vs. 156.1±8.2 cm; p=0.00657). The TJCs and DAS28-CRP values in the Bio-free group (n=20) were significantly lower than those in the non-Bio-free group (3.5±5.26 vs. 5.0±4.3, p=0.00741; 3.5±1.3 vs. 4.1±1.2, p=0.0254, respectively). The mHAQ of the Bio-free group (n=20) was significantly lower than that of the non-Bio-free group (0.313±0.436 vs. 0.577±0.48, p=0.0492).

However, when we evaluated the patients who were able to discontinue ADA (n=26, including the 6 who could not be followed up for 6 months after the discontinuation of ADA) with non-Bio-free patients (n=104), for some reason, the differences in the MTX and mHAQ lost significance.

A comparison of the Bio-free (n=20) and non-Bio-free patients (n=104) by a multivariate analysis

A multivariate analysis showed the dose of MTX to be an important factor associated with a Bio-free condition (Table 2).

When the dose of MTX was increased to 1 mg or more/week at the introduction of ADA, then the patients were able to achieve a Bio-free state at a rate 1.26 times higher than the original dose of MTX (Table 2).

The changes in the DAS28-CRP values in the Bio-free and non-Bio-free groups

Fig. 1 shows the changes observed in the DAS28-CRP values in the Bio-free and non-Bio-free groups plotted by the last observation carried forward (LOCF) method (n=20 and n=104).

The number of ADA-treated patients is indicated with squares. The last observed data of the patients who stopped ADA due to side effects (n=13), primary failure (n=14), secondary failure (n=6), and those who were Bio-free (n=17) were used after the discontinuation of ADA.

At baseline and at 24 months, the DAS28-CRP values in the Bio-free group were significantly lower than those in the non-Bio-free group (3.53±1.36 vs. 4.11±1.19, p=0.0254, 1.63±0.52 vs. 2.46±1.11, p<0.001).

The DAS28-CRP values were significantly ameliorated from baseline to 24 months in both groups [3.53±1.36 to

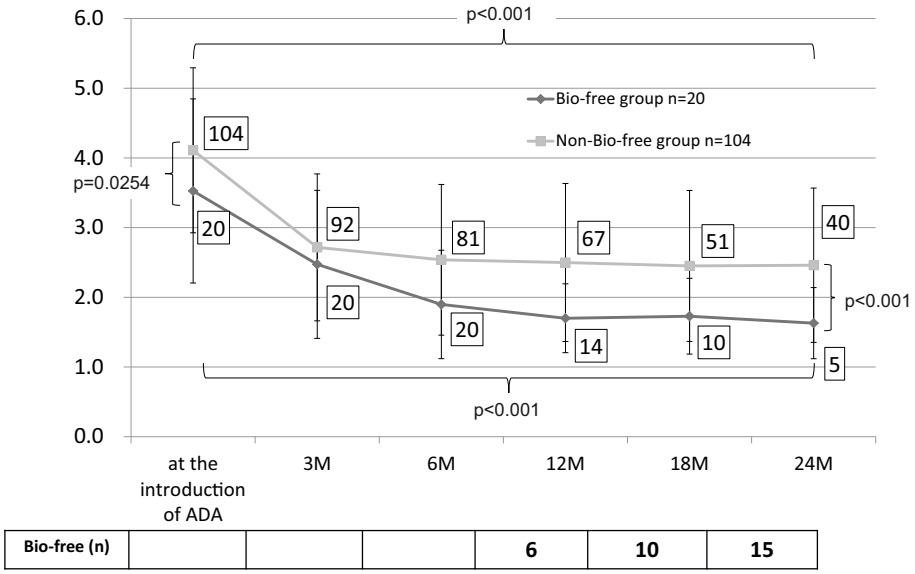

Figure 1. **Changes in the DAS28-CRP after the introduction of adalimumab in the non-Bio-free (n=104) and Bio-free patients (n=20) using adalimumab by the last observation carried forward (LOCF) method. The number of patients treated with adalimumab is shown in the squares. The DAS28-CRP values were compared at baseline and 24 months by the Wilcoxon signed-rank test. Differences between the Bio-free and non-Bio-free groups were assessed using the Mann-Whitney U test. ADA: adalimumab, DAS28-CRP: disease activity score 28 based on C-reactive protein, LOCF: last observation carried forward methods**

1.63±0.52 (Bio-free group: p<0.001) and 4.11±1.19 to 2.46±1.11 (non-Bio-free group: p<0.001)].

The clinical course of the Bio-free group patients who were followed for more than 6 months (n=20)

One female patient who had a flare-up of RA (Loss of CR, DAS28-CRP: 2.48) and re-started ADA, ultimately achieved a CR again. She then wanted to enter a Bio-free condition again; thus, we added tacrolimus (TAC) and discontinued ADA again. She maintained a CR without ADA for 22 months. Thus, all of the patients with a Bio-free condition maintained a Bio-free condition. The average Bio-free period at the time of the study was 26.4±15.5 months. As mentioned above, the average duration of ADA usage until a Bio-free condition was achieved was 17.7±8.0 months. Five patients discontinued ADA after maintaining a CR for more than 2 years; however, 15 patients discontinued ADA before then due to financial reasons. The shortest period of ADA usage was four months. The average CR duration was 13.4±8.1 months. For some reason, one patient who discontinued ADA with LDA achieved a CR, 24 months after the discontinuation of ADA without any change in treatment.

Fig. 2a shows the DAS28-CRP values of the Bio-free patients treated with and without ADA. The number of patients without ADA (Bio-free patients) was plotted. Although we proposed that the patients consider trying to achieve a Bio-free condition after 2 years of CR (as mentioned above), 15 patients discontinued ADA at 24 months due to financial reasons. However, the DAS28-CRP values of the patients who discontinued ADA did not worsen.

The DAS28-CRP values were significantly ameliorated at 24 months after the introduction of ADA in comparison to the values observed at the start of ADA, with or without ADA (3.52±1.35 to 1.51±0.45, p=0.000111).

Fig. 2b shows the DAS28-CRP level of the Bio-free patients when they discontinued ADA.

Disease activity after becoming Bio-free

At 6 months after the discontinuation of ADA, 18 patients maintained a CR, 1 patient with LDA achieved a CR (as mentioned above), and 1 patient with a CR developed LDA.

At the last observation, 18 patients had maintained a CR, and 1 had LDA (the DAS28-ESR value was consistent with LDA) and 1 patient had MDA (DAS28-ESR value was consistent with MDA). The longest period for which a patient was observed in a Bio-free condition was 57 months (with CR).

The doses of prednisolone (PSL), MTX, and the numbers of csDMARDs other than MTX in the Bio-free group (Fig. 3)

The dose of PSL in the Bio-free group was significantly reduced from baseline (3.45±3.17 mg/day) to 6 months after the discontinuation of ADA (2.63±2.78 mg/day) (p=0.0037, Fig. 3a). Among the Bio-free group patients who were treated with PSL (n=14), the dose of PSL was also significantly reduced from baseline to 6 months after the discontinuation of ADA (from 4.93±2.66 to 4.77±1.95 mg/day, p=0.0137). However, the dose of MTX in the Bio-free group did not markedly change from baseline to 6 months after the

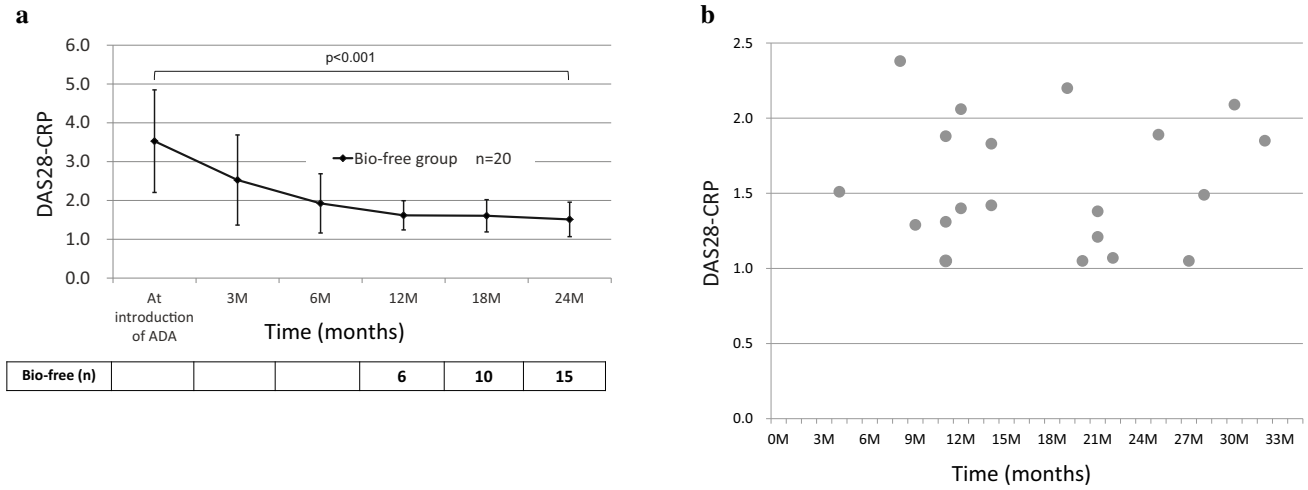

Figure 2. **a: Changes in the DAS28-CRP values after the introduction of adalimumab in the Bio-free group with and without the use of adalimumab. The number of Bio-free patients is shown in the lower boxes. The DAS28-CRP values at baseline and 24 months were compared in patients who had achieved or who were going to achieve a Bio-free condition. b: The DAS28-CRP level of the Bio-free patients when they discontinued adalimumab. ADA: adalimumab, DAS28-CRP: disease activity score 28 based on C-reactive protein**

discontinuation of ADA (Fig. 3b). The number of csDMARDs other than MTX was significantly increased from baseline to 6 months after the discontinuation of ADA (from 0.8±0.6 to 1.4±1.06, p=0.00352) (Fig. 3c).

Changes in csDMARDs other than MTX

At the introduction of ADA, 14 patients were taking csDMARDs other than MTX. Twelve patients were taking one csDMARD and two patients were taking two csDMARDs. The csDMARDs that were prescribed were as follows: bucillamine (BUC), n=8; mizoribine (MZR), n=3; sarazosulfapyridine (SASP), n=3; and TAC, n=2. At 6 months after the discontinuation of ADA, 16 patients were taking csDMARDs other than MTX. Eight patients were taking 1 csDMARD, 5 patients were taking 2, 2 patients were taking 3, and 1 patient was taking 4. BUC was used by 5 patients, MZR by 10, SASP by 5, and TAC by 6. Iguratimod was newly started in two patients. One patient with BUC developed proteinuria; thus, BUC treatment was discontinued; the proteinuria disappeared within six months after the discontinuation of BUC. Another patient with BUC developed yellow nail syndrome, which led to the discontinuation of BUC; the patient's yellow nail syndrome disappeared within 12 months after the discontinuation of BUC.

With regard to the timing of the addition of csDMARDs, csDMARDs were added at 9.7±6.2 months before the discontinuation of ADA in 6 cases, at the time of discontinuation in 4 patients, and after the discontinuation of ADA (4.3±2.7 months) in 6 patients. Two csDMARDs were added both before and after the discontinuation of ADA in 1 patient.

Changes in the DAS28-CRP values of the Bio-free group

Fig. 4 shows the changes in the DAS28-CRP values of the Bio-free group. A low DAS28-CRP was maintained. At 24 months after the discontinuation of ADA, the DAS28-CRP was not significantly changed (n=8; Wilcoxon signed-rank test, p=0.08). The number of patients is plotted in the square.

Changes in the mHAQ after achieving a Bio-free condition

Fig. 5a shows the changes in the mHAQ scores after achieving a Bio-free condition. The mHAQ scores at six months after the discontinuation of ADA were significantly lower than the scores at baseline. Fig. 5b shows the rate of mHAQ remission after achieving a Bio-free condition. With the introduction of ADA, each patient achieved an mHAQ remission, which was maintained for 6 months after the discontinuation of ADA.

Regarding the efficacy of adding csDMARDs on the maintenance of CR: The analysis of the last observation.

At the last observation, the number of csDMARDs in the Bio-free group was significantly greater (1.4±1.07) than in the non-Bio free group (0.82±0.89, p=0.0213). At the last observation, 11 patients in the Bio-free group were still using PSL. However, the dose of PSL in the Bio-free group at the last observation (2.25±2.27 mg/day) was significantly lower than at 6 months after the discontinuation of ADA (2.63±2.78 mg/day, p=0.0035). The dose of PSL in the Bio-free group at the last observation (2.25±2.27 mg/day) was

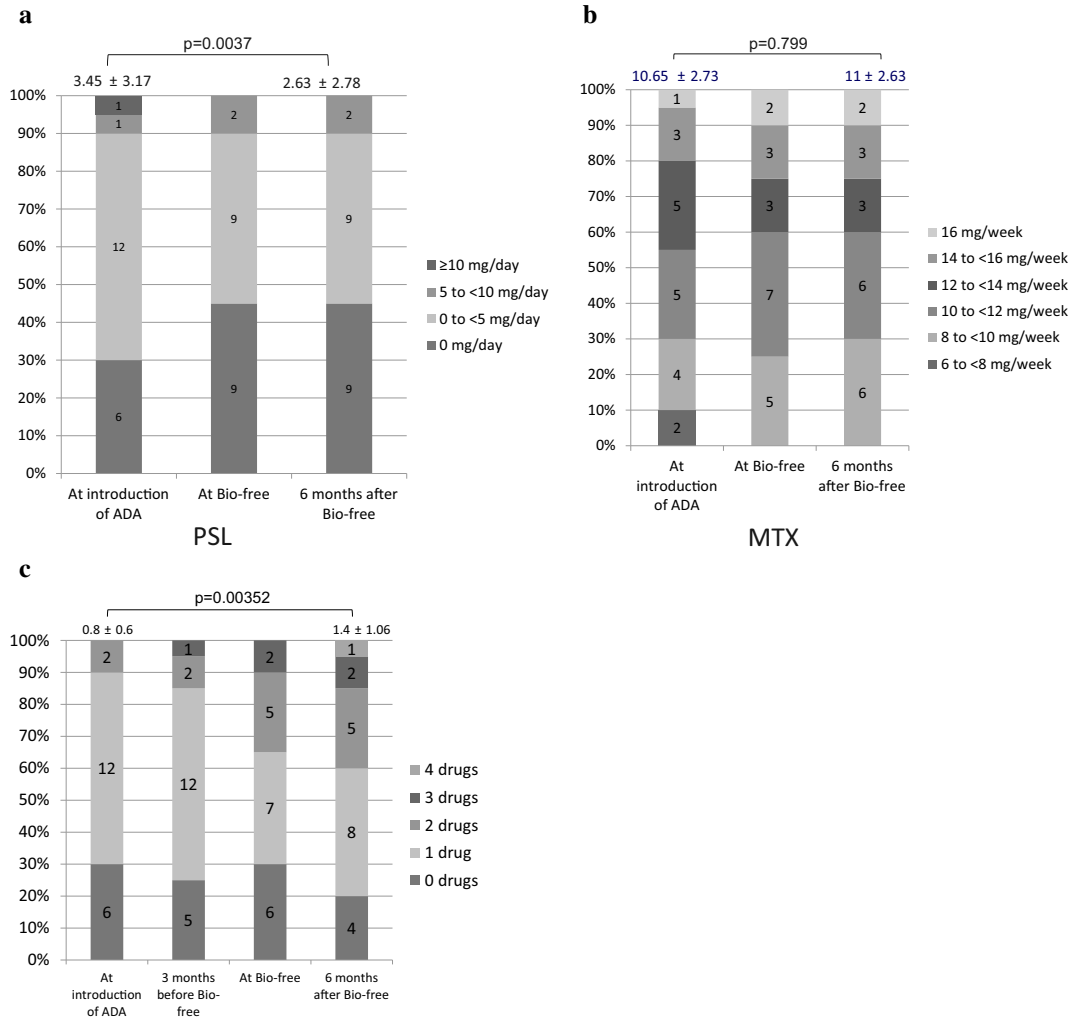

Figure 3. **(a) The changes in the dose of PSL, (b) MTX, and (c) the number of csDMARDs other than MTX at the introduction of ADA, at the achievement of a Bio-free condition, and six months after this achievement. ADA: adalimumab, PSL: prednisolone, MTX: methotrexate, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs**

lower than that in the non-Bio-free group (2.74±2.51 mg/day), but no significance was observed (p=0.432). Four patients who started csDMARDs simultaneously after reaching a Bio-free state did not require additional csDMARDs (0/4, 0%), while 6 patients did need additional csDMARDs after achieving a Bio-free state among the 16 who did not start csDMARDs simultaneously after achieving a Bio-free state (6/16, 37.5%), with no significance (p=0.542).

Discussion

With the introduction of bDMARDs, RA patients can achieve and maintain a CR in the clinical setting (15). However, bDMARDs are extremely costly, and this expense has become a global issue (16). After achieving and maintaining a CR for a certain period, bDMARDs can be discontinued and a CR can be maintained with IFX and ADA (5-9). However, Smolen et al. concluded that in patients with established RA, the frequent stopping of biological agents can lead to a loss of LDA or remission. In contrast, dose reduction or the spacing of application intervals is associated with less a risk of a relapse (10).

In this study, our findings showed that 20.0% of RA patients were able to discontinue ADA and maintain a good condition. One patient had a flare-up after the discontinuation of ADA; however, she re-started ADA, achieved a CR again and was able to maintain a CR with the addition of TAC. Thus, all patients are still in a Bio-free condition, despite their long disease duration (42.4±15.1 months). We consider that a Bio-free condition can be achieved even in patients with established RA. According to Table 1 and Fig. 1, the disease activity might be a key to achieving a Bio-free condition since the DAS28-CRP and TJC values of the Bio-free group were higher than those of the non-Bio-free group.

In addition, we believe that our good results were achieved due to our medical practices. Recently, we have been combining an adequate amount of MTX with ADA (4). When ADA was introduced in Japan in April 2008, since ADA was a fully humanized antibody, it was suspected that

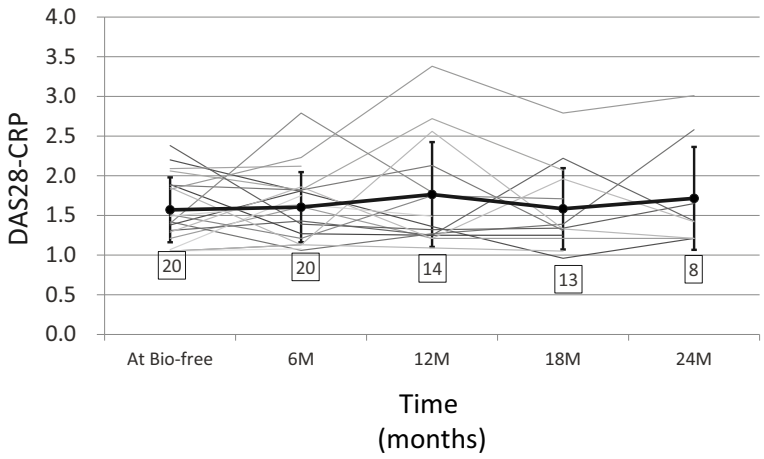

Figure 4. **Changes in the DAS28-CRP values after achieving a Bio-free condition. DAS28-CRP: disease activity score 28 based on C-reactive protein**

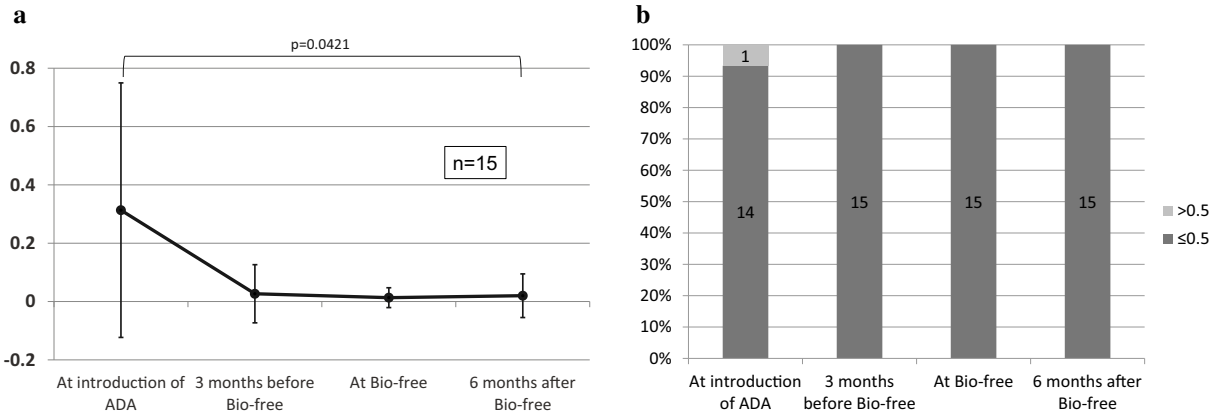

Figure 5. **(a) Changes in the modified Health Assessment Questionnaire after achieving a Bio-free condition. (b) The remission rate (according to the modified Health Assessment Questionnaire) after achieving a Bio-free condition. The number of patients is shown in the squares. ADA: adalimumab**

patients with ADA seldom produced anti-ADA antibodies. As such, a large number of patients received ADA monotherapy or only low-dose MTX treatment, and the efficacy of ADA was very low (4). Once it was recognized that ADA needed to be administered with an adequate amount of MTX, we only recruited patients who would use ADA with an adequate amount of MTX; the recent results of ADA treatment have been very good (4). Since the present Bio-free analysis analyzed all patients who received ADA at two hospitals and one clinic (where the first author worked), we hypothesize that the percentage of patients who achieved a Bio-free condition improved with the inclusion of an adequate dose of MTX. We now never administer ADA without an adequate amount of MTX, with the aim of further improving the Bio-free condition of ADA-treated patients in the future.

Furthermore, the multivariate analysis clarified that the dose of MTX when starting ADA was an important factor for achieving a Bio-free condition.

Another reason for the good results regarding the numbers of patients who could achieve a Bio-free condition in our study may be the use of csDMARDs other than MTX. There have been reports of triple therapy with csDMARDs, and the clinical results were as good as those obtained with MTX+TNF inhibitors (17-20). Since the effects of csDMARDs appear more slowly than those of MTX+TNF inhibitors, the clinical response of the triple therapy was comparable to that of MTX+TNF inhibitors, except for the fact that there were some differences in the degree of joint destruction (17, 18). It should be noted that the findings of O'Dell's and Matsuno's studies did not indicate that the effects of csDMARDs appear more slowly than those of MTX +TNF inhibitors (19, 20). In our study, we used ADA with MTX and increased the number of csDMARDs, with the aim of administering triple csDMARD therapy. Although we did not analyze joint destruction, this tactic might be good and thus should be investigated further. It has already been reported that adding csDMARDs can achieve good results under Bio-free conditions. When IFX was discontinued, the addition of BUC achieved better results, especially in rela-

tion to maintaining a Bio-free condition (21). In addition, it was reported that csDMARDs other than MTX inhibit the formation of anti-ADA antibodies (22), which may reinforce the effects of ADA.

As Smolen et al. reported, the results of Bio-free patients were not very good (10), with 21/50 (42%) and 27/52 patients (52%) losing CR according to the DAS28-ESR at 6 months and 1 year, respectively, after the discontinuation of ADA (7, 8). In our study, 18/20 patients (90%) maintained CR as judged by the DAS28-CRP at 6 months after the discontinuation of ADA and at the last observation, a difference we attribute to the addition of csDMARDs. Of note, the dose of PSL at the last observation was further reduced compared with the PSL dose at six months after the discontinuation of ADA.

In our study, we used both immunomodulatory and immunosuppressive csDMARDs, and both seemed to work well. We should clarify which type of csDMARDs is most appropriate for maintaining a Bio-free condition with more patients in the future.

Eleven patients in the Bio-free group did not discontinue PSL at Bio-free or at the last observation, although the dose of PSL was further reduced after the discontinuation of ADA. The EULAR recommends tapering of bDMARDs after the tapering of steroids (23). Schett et al. also insisted that the Bio-free condition should be steroid-free (24). Therefore, we have recently recommended that patients discontinue ADA after stopping PSL; however, for financial reasons or out of fear of relapse, some patients prefer to discontinue ADA with low-dose PSL.

The present study is associated with some limitations. Most notably, it was not a prospective study. Furthermore, there were no criteria for the discontinuation of ADA. Many patients wanted to enter a Bio-free condition despite a short period of CR for financial reasons. In fact, only 5 patients continued ADA after achieving a CR for more than 2 years. Other patients wanted to discontinue ADA earlier due to financial reasons. We must therefore take this into account when we compare the Bio-free and non-Bio-free groups. However, we believe that we were able to show a high percentage of Bio-free patients. Furthermore, we demonstrated the successful maintenance of a Bio-free condition in a real-world setting. Seventy-one patients continued ADA. Among them, 15 were covered due to the welfare system for the handicapped or single mothers. Thus, they did not need to discontinue ADA for financial reasons. As mentioned above, since it has already been reported that the continuous use of ADA results in a better outcome than an ADA-free condition (7-9), we did not suggest that they discontinue ADA.

Since we wanted to use the same criteria for the disease activity across all study sites, we used the DAS28-CRP in order to incorporate the data from the Ishii Clinic. However, the treatment decisions of the rheumatologists at Niigata Rheumatic Center and Niigata Prefectural Kamo Hospital might have been made based on the DAS28-ESR.

We now use the Health Assessment Questionnaire-Disability Index (HAQ-DI); however, when ADA treatment was started at our rheumatic center, only the mHAQ was recorded. In addition, the mHAQ was not recorded at Niigata Prefectural Kamo Hospital or Ishii Clinic; thus, only limited mHAQ data were available during the study period.

In conclusion, we herein presented the outcomes of Bio-free patients treated with ADA in a real-world setting. Thus far, all of the patients have maintained a Bio-free condition. This approach might be a good choice in terms of reducing the total medical cost in the long term. The additional use of csDMARDs before and after the discontinuation of bDMARDs is thought to be important for successfully maintaining a Bio-free condition without a disease flare-up.

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Author's disclosure of potential Conflicts of Interest (COI).
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