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Effects of Adalimumab Administration in Bio-Naïve and Bio-Switch Rheumatoid Arthritis Patients in Daily Clinical Practice : Two-Year Results from Single Center

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Abstract

Aims : To investigate the impact of adalimumab on the biologic-naïve (bio-naïve) and bio-switch rheumatoid arthritis (RA) patients, and to clarify the appropriate indications for adalimumab treatment.

Methods : The retention rate, efficacy and safety of adalimumab in twenty-one RA patients were analyzed. Fourteen of the patients were bio-naïve and seven were bio-switched from other biologics. Concomitant methotrexate was used in 85% of the bio-naïve and 71% of the bio-switch patients. The radiographic findings before and after the 1 year and the two years treatment were also surveyed.

Results : In the bio-naïve group, 63% of patients continued adalimumab for 2 years, and remission was achieved in approximately 50% of patients. The mean 28-joint Disease Activity Scores improved from 5.2 to 2.6. Radiographically, the joint damage did not progress in either erosions or joint space narrowing. In the bio-switch group, the retention rate was 29%, and only patients who were switched from infliximab showed responses to the treatment. Herpes zoster requiring hospitalization occurred in two cases and injection site reactions were noted in other two cases.

Conclusion : Adalimumab combined with methotrexate would be a useful first choice biologic regimen in bio-naïve RA patients. As a second biologic, adalimumab could be useful only when treatments are switched from infliximab.

Key words : Adalimumab・Biologic-naïve・Methotrexate・Observational study,・Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) induces joint destruction, which decreases physical ability and / or activities of daily living (ADL) for patients. To avoid these effects, early, appropriate and aggressive treatment is important. There have been several previous reports about different biological agents which have been developed and used in clinical trials to block arthritis, induce and maintain remission, and to prevent further joint destruction[1)~9)].

Adalimumab (ADA) is a fully human anti-tumor necrosis factor-alpha (TNF-α) monoclonal antibody. ADA inhibits the transfer of the TNF-α signal to TNF-targeted cells, and exerts potent anti-inflammatory effects not only by inhibiting the conjugation of TNF-α to its receptors, but also by dissociating conjugated TNF-α from its receptors[10)]. ADA is administered via subcutaneous injection, making it possible to use it in an outpatient clinic, thus resulting in a stable patient retention rate and high efficacy in RA treatment. There have been several previous reports of the effects of ADA in clinical trials[11)~15)]. However, there have been only a few reports with relatively short term follow-up period within 1 year from multi-center observa-

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tional studies that have investigated the safety and efficacy and indications for ADA in daily practice in Asian RA patients[16)17)] and there have been no report with two-year follow-up from single center.

The goal of this study was to clarify the appropriate indications for ADA treatment in biologic-naïve (bio-naïve) or bio-switch (switched from a previous biologic agent) Asian RA patients by investigating the efficacy and retention rate of ADA during RA treatment.

Patients and Methods

Treatment

From January 2009 to June 2011, 21 consecutive RA patients who had an insufficient response to DMARDs therapy were prescribed 40 mg of subcutaneous ADA to be administrated every other week in the Department of Orthopaedic Surgery in Kyushu University Hospital. All of the patients enrolled in this study fulfilled the American College of Rheumatology (ACR) 1987 criteria for the classification of RA. Fourteen of these patients were bio-naïve (two males and 12 females) and seven of them were bio-switch patients (all female). In the bio-naïve group, the mean age was 53 years, while in the bio-switch group, it was 67 years (Table 1). The breakdown of the previous biologic agents used in the switched patients includes secondary lack of efficacy (LOE) to infliximab (IFX) in 3 cases, etanercept (ETN) in 2 cases, tocilizumab (TCZ) in 1 case and IFX and TCZ in 1 case. In both groups, if methotrexate (MTX) could be used, it was added to the treatment.

Evaluation methods

The drug retention rate was calculated by the Kaplan-Meier estimate, and the reasons why some patients dropped out were investigated. Clinical items such as the tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF) and matrix metalloproteinase-3

Table 1 Baseline data

	Bio-naïve	Switch
n	14	7
Gender		
Male	2	0
Female	12	7
Mean age	53 (33～73)	67 (52～78)
Disease duratiom (years)	8.1 ± 9.6	14.2 ± 8.6
	I/II/III/IV	I/II/III/IV
Stage	3/4/3/4	0/1/1/5
Class	0/8/6/0	0/3/4/0
TJC / 28	6.9 ± 4.8	4.9 ± 3.4
SJC / 28	7.2 ± 3.5	4.7 ± 1.8
VAS (/100 mm)	50.5 ± 20.4	65.9 ± 34.6
CRP (mg/dL)	2.0 ± 2.3	2.4 ± 1.8
ESR (mm/hr)	39.8 ± 27.1	52.7 ± 29.9
MMP-3 (ng/mL)	231.9 ± 205.4	363.1 ± 470.6
RF positive	12/14 (86%)	7/7 (100%)
RF value (IU/mL)	307.6 ± 477.5	496.9 ± 376.5
Concomitant MTX	12/14 (86%)	5/7 (71%)
MTX dose (mg)	6.6 ± 3.4 mg	5.7 ± 3.3 mg
Concomitant PSL	7/14 (50%)	7/7 (100%)
PSL dose (mg)	2.1 ± 2.3 mg	4.9 ± 2.6 mg

* : Steinbrocker's therapeutic criteria in rheumatoid arthritis.
TJC : tender joint count, SJC : swollen joint count, VAS : visual analogue scale, RF : rheumatoid factor, ESR : erythrocyte sedimentation rate, MTX : methotrexate, PSL : prednisolone

(MMP-3) levels, the patient visual analog scale (VAS) pain score, the physician VAS score, and so on were evaluated every three months, and the treatment response rate was calculated as the 28-joint Disease Activity Scores (DAS28)-ESR and the ACR20, 50, 70. In addition, the remission achievement rate was calculated based on a standard using the DAS28-ESR and Boolean scores. To evaluate the safety of the treatment, the incidence of adverse events was investigated and reported as events per 100 patient-years. The association of these effects with adalimumab was surveyed. It was also determined whether any hospitalization was required for these events and whether any cases required termination of treatment. The radiographic evaluation was based on the Sharp's score using both hand X-rays at baseline, 1 year and 2 years after treatment[18]. Briefly, 27 areas of each hand and wrist were scored for erosions and joint space narrowing (JSN). The severity of erosions were scored from 0 (normal) to 5 (more than one half of articulating bone is involved) in each joint and summed up as the erosion score (ES). JSN was ranked from 0 (normal) to 4 (ankylosis) and summed up as the JSN score.

This study protocol was reviewed and approved by the institutional review board, and all patients gave their informed consent before they were included.

Statistical analysis

The drug retention rate calculated by the Kaplan-Meier estimate was compared by the log-rank test. To determine the differences in the continuous variables (such as the DAS28-ESR score and biochemical markers) at different times, we used a one-way factorial ANOVA with Fisher's protected least significant difference post-hoc test. The data of the DAS28-ESR score and the Sharp's score was analyzed by the last observation carried forward (LOCF) method. An unpaired t-test was used to compare the DAS28-ESR score between the bio-naïve group and the switch group. Differences in the total percentage of ACR50 and 70 between the two groups were determined by the Mann-Whitney U test. A paired t-test was used to compare the mean erosion score (ES) and the joint space narrowing (JSN) score in X-rays before the initiation of ADA and after the treatment. In order to appropriately calculate the mean values and perform comparisons of the changes in biochemistry data, the calculations were performed just in patients who could continue the treatment.

Results

The retention rate in the bio-naïve group, which was 79% at one year and 63% at 2 years, was relatively stable, whereas the rate in the switch group was low, 43% at 6 months and at 29% after 1 year, due to a high lack of efficacy (Fig. 1), and this difference was statistically significant ($p < 0.05$). The reasons for discontinuation were adverse events in two cases (14.3%), secondary failure in two cases (or acquired therapeutic resistance) (14.3%) and one patient stopped the treatment for economic reasons (7.1%) in the bio-naïve group, whereas in the switch group, the reasons were secondary failure (or acquired therapeutic resistance) in three cases (42.9%) a lack of efficacy in one case (14.3%) and an adverse event in one case (14.3%).

The DAS28-ESR score, an index of the disease activity, was high in both groups at baseline (>5.2), but in the bio-naïve group was indicative of remission (< 2.6) or low disease activity (< 3.2) as early as three months after treatment. In the bio-switch group, two of three cases who switched to ADA due to a secondary LOE of infliximab (IFX) were able to continue ADA for more than three years, and showed a good response in terms of the disease activity, but their mean DAS28-ESR score did not improve from the baseline values because other cases of the bio-switch group discontinued ADA with a moderate to high disease activity (Fig. 2). The

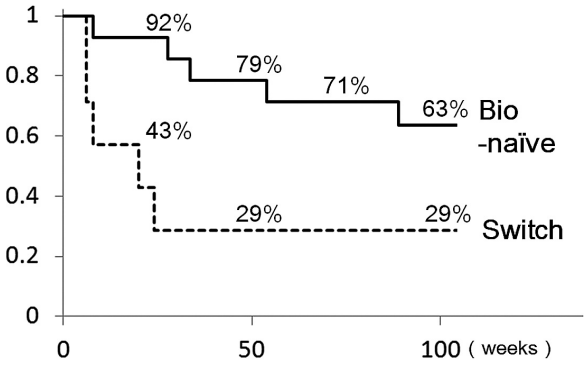

Fig. 1 The drug survival rates for adalimumab in the bio-naïve group and bio-switch group are shown. The retention rate in the bio-naïve group was significantly higher in the bio-naïve group ($p < 0.05$).

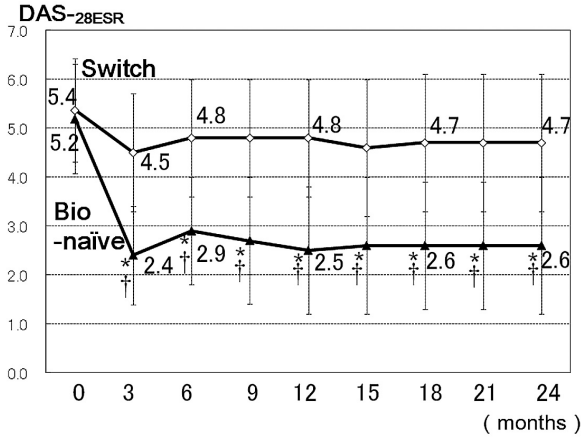

Fig. 2 The time course of the disease activity (DAS28-ESR) score over an 24 month period following the initiation of adalimumab treatment is shown. Points and full lines represent the means. Dotted bars represent the standard deviations. The data were analyzed by the last observation carried forward (LOCF) method. * : $p < 0.01$ compared with zero months. † : $p < 0.05$ compared with the bio-switch group.

mean DAS28-ESR score in the bio-naïve group was significantly lower than in the bio-switch group throughout the time course after 3 months ($p < 0.01$).

In the bio-naïve group, ACR50 and 70 responses were achieved by 77% of patients at six months and 1 year, respectively, and those responses were maintained by 57% of the patients at 2 years. In the switch group, the results were 29% and 14% at six and 12 months, and 29% at 2 years (Fig. 3). There were significant differences in the total percentages of ACR50 and 70 between the two groups at 3, 6, 9 and 12 months ($p < 0.05$), but no statistical difference was detected after 15 months.

The remission achievement rates according to the DAS28-ESR score were 64.3% and 50.0% at 1 and 2 years in the bio-naïve group (Fig. 4a). In the bio-switch group, only one patient (14. 3%) achieved remission. The Boolean remission score (including the swollen joint count, tender joint count < 1, and patient VAS < 1 cm), which is a very strict measurement, showed a gradual improvement in the bio-naïve group, and almost half of the patients achieved and maintained Boolean remission after one year (Fig. 4b).

The CRP level decreased from 2.1 ± 2.5 mg/dL at baseline to 0.3 ± 0.5 mg/dL three months after treatment ($p < 0.01$), and the MMP-3 level significantly decreased from 152.1 ± 107.0 ng/dL at baseline to 78.7 ± 64.8 ng/dL three months after starting ADA treatment in the bio-naïve group ($p < 0.05$). After six months, the CRP and mean MMP-3 levels continued to show decreased levels (Fig. 5a). On the other hand, the impact on RF in the bio-naïve group was inconsistent, with some patients showing a major decrease, while it did not change in other cases, therefore, there was no significant change in the RF. In the bio-switch group, no significant difference was observed in the time course of the CRP, the MMP-3 and the RF levels (Fig. 5b). There were a few adverse events that developed, such as injection site reactions, herpes zoster reactivation, chest X-ray abnormalities and breast cancer (Table 2). Active tuberculosis, demyelinating disease and systemic lupus erythematosus did not occur in any of the patients in the present study.

In the radiographic evaluation, joint damage in the hands and wrists had not progressed at 2 years in the bio-naïve group. In this group, the erosion score (ES) decreased from mean 33.5 at baseline to 31.8 after 1 year ($p < 0.05$) and it was maintained to be 31.7 at 2 years. There was local (focal) bone repair of erosions in several cases (Fig. 6) The joint space narrowing (JSN) score at

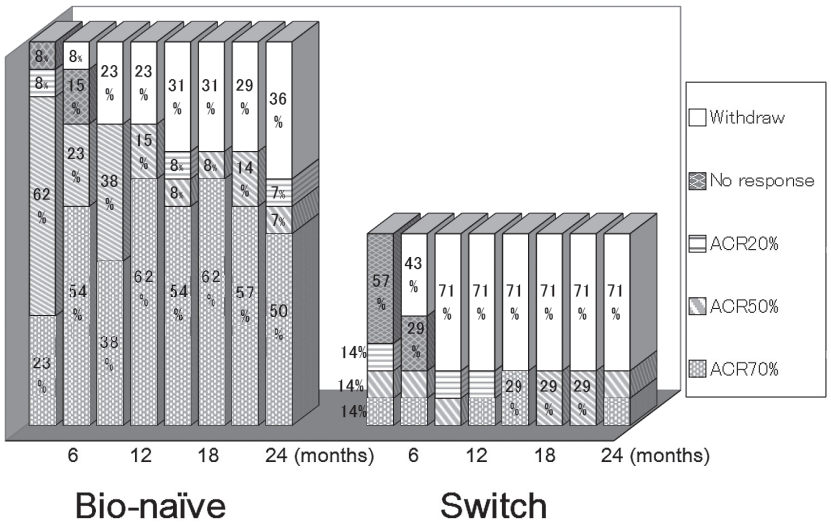

Fig. 3 The time course of ACR responses over the 24 month period following the initiation of adalimumab treatment is shown. The majority (77%) of patients in the bio-naïve group achieved ACR50 and 70 responses at 12 months, and 57% maintained these responses at 24 months. In the bio-switch group, the rates of ACR50 and 70 responses were less than 30% throughout the study period. There were significant differences in ACR50 and 70 responses between the two groups at 3, 6, 9 and 12 months ($p < 0.05$).

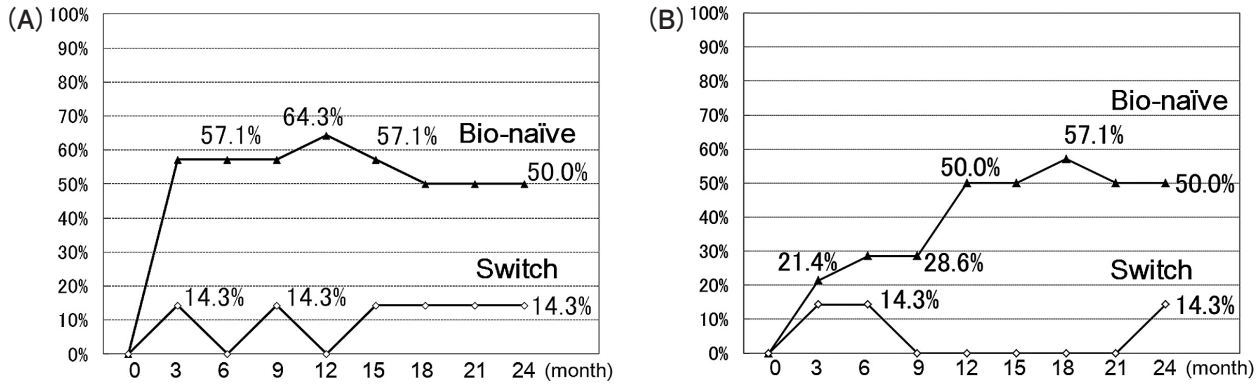

Fig. 4 The percentages of patients who achieved clinical remission are shown. (A) A DAS28-ESR < 2.6 was considered to indicate remission. Almost half of the bio-naïve patients reached remission by three months and maintained it until 24 months. (B) The remission rate based on the Boolean definition is shown. In the bio-naïve group, the rate increased gradually, and almost half of patients had reached and maintained remission after 12 months.

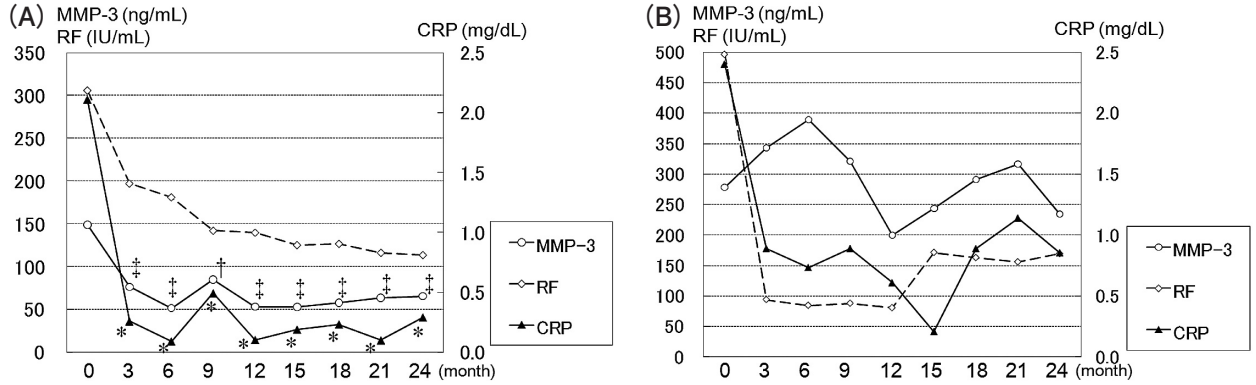

Fig. 5 The time course of biochemical markers is shown. (A) In the bio-naïve group, the CRP and MMP-3 levels substantially decreased after the initiation of adalimumab treatment. The RF level did not show a significant change, although some cases showed a large decrease. *, ‡: $p < 0.01$ compared with before treatment. †: $p < 0.05$ compared with before treatment. (B) In the bio-switch group, no significant difference was observed in the time course of the CRP, the MMP-3 and the RF levels.

Table 2 Adverse events

	n	Events/100 patient-years	Severe events (requiring hospitalization)	Discontinuation	Causal relationship
Injection site reaction	2	4.8	0	1	Possible
Herpes zoster	2	4.8	2	0	Possible
Chest X-ray abnormality	1	2.4	0	1	Unclear
Breast cancer	1	2.4	1	1	Unclear

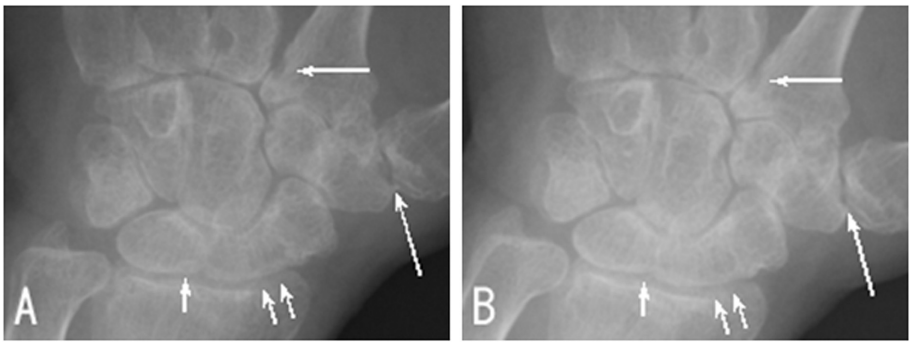

Fig. 6 The left hand joint radiographic appearance of a 61-year-old female with RA is shown. (A) Joint space narrowing and a lot of bone erosion can be observed in the radio-carpal joints and carpo-metacarpal joints. (B) Twelve months after treatment with adalimumab, the area of the bone erosion was reduced, and improvement of the bone absorption can be observed.

baseline was 42.0, and 42.1 and 42.1 at 1 year and 2 years, which indicated that there was a blockade of disease progression. In the bio-switch group, although follow-up x-ray films throughout the 2 years were obtained in only one patient with mostly low disease activity, but this case showed the blockade of joint destruction with ES scores of 54, 55 and 52 and JSN scores of 64, 65 and 65 at baseline, 1 year and 2 years.

Discussion

Several biological agents have been advocated to tightly control the disease activity in RA and prevent joint destruction. Adalimumab is a fully human anti-TNF- α monoclonal antibody agent which is suitable for use in outpatient clinics. Recently, several randomized clinical trials (RCT) from multi center have reported the safety and efficacy of ADA treatment for active RA[11)~15)]. However, observational cohort studies are also very important, because in daily practice, rheumatologists have to care for RA patients who have concomitant illnesses and are taking various medications, as well as who have different backgrounds, which can make it more difficult to select the treatment method and decide which drugs should be continued[19)]. In addition, only a few studies with relatively short term follow-up period of 24 weeks to 1 year from multi-center have investigated ADA use in daily practice in Asian RA patients[16)17)]. This study examined two-year results of the efficacy and continuation rate of RA patient treatment with ADA in daily practice from single center, and also investigated the indications for treatment with ADA.

According to the results of our daily practice experience, a stable treatment continuation rate and a good treatment response, as well as durable remission and low disease activity was shown in the bio-naïve group. Such bio-naïve patients can expect a high continuation rate and efficacy of ADA as the first biologic agent. The four-year extended study included in the ARMADA trial, which investigated the long term efficacy and safety of ADA plus MTX for patients with RA, reported a high retention rate of 87% at 1 year and 79% at 2 years, and a satisfactory ACR50/70 response rate of over 50% at 1 year[12)]. The Danish

DANBIO registry, which compared ADA, ETN and IFX directly in a total of 2326 RA patients showed the superiority of ADA and ETN in terms of their efficacy at six and 12 months and in the continuation rates at 12, 24 and 48 months, compared to IFX[20]. These high retention rates are highly desirable as the first biologic agent and have been attributed to the fact that neutralizing antibodies develop less often in patients treated with combination therapy using MTX[11)21)]. The relatively low frequency of severe adverse events, including anaphylactic infusion reactions, is another reason for the stable continuation[22]. According to our experiences, severe adverse events which required hospitalization that could have been due to ADA occurred in only two cases (4.8/100 patient-years), both of which developed herpes zoster, and no serious infusion reactions or tuberculosis were seen in our patients.

The CRP and mean MMP-3 levels significantly decreased from baseline after starting ADA treatment in the bio-naïve group. Previous studies about immunohistological examination have reported that the expression of cytokines and MMP-3 were decreased in synovial tissues treated with ADA or other anti-TNF therapies[23)~25)].

Although a previous observational study showed a considerable response and effectiveness of ADA in RA patients with a history of TNF-antagonist therapy at 12 weeks[26], in our experiences, the continuation rate in the switched cases was relatively low, and the failures of treatment generally occurred early, which led to a high dropout rate. However, when we investigate the breakdown of the previous biologics used in the switched patients, we noted that two of the three patients with secondary LOE to IFX showed a good response to the continuation of ADA over a period of three years. According to the post-marketing surveillance of ADA in 3000 active RA patients in Japan, the cases switched from IFX also showed a good response at 24 weeks[16]. On the other hand, an observational study on 2242 active RA patients who received anti-TNF treatment, which was based on a USA registry, reported that dose/frequency escalations of IFX resulted in greater persistence and maintained response and remission outcomes[27]. According to our data and these previous reports, when cases of secondary failure of IFX are encountered, dose/frequency escalations or switching to ADA should be considered. In the present study, we had only two patients who switched from ETN to ADA, both of whom required early termination due to a lack of efficacy. According to an observational study of 479 cases switched from various anti-TNF preparations, a switch from IFX to ADA or ETN, or from ADA to ETN restored the initially achieved response to the first TNF blocker, but when patients were switched from ETA to ADA, improvement of the disease activity score was not seen[28]. Theoretically, after a long duration of anti TNF receptor administration, it is assumed that patients will have an excess situation of serum TNF- α, which is likely to lead to a lack of response to further treatment.

When we explored the X-ray findings to determine whether there was a blockade of bone erosion or joint space narrowing (JSN) progression, this study confirmed that there was no progression in the number of bone erosions or the JSN, although the present study duration was only 24 months in the bio-naïve group. In addition, local bone erosion repair was observed in some cases. There has been one study that included X-ray evaluations of patients treated with IFX, which showed that bone erosion and JSN changes are independent elements[29]. Another study by micro CT after one year of anti-TNF and MTX combination therapy showed that bone erosions were repaired[30]. In another study, after one year of ADA and MTX combination therapy, no progression in X-ray changes and occasional repair of bone erosions were reported[31]. Therefore, the prevention of joint destruction can occur following treatment with an anti-TNF agent and

MTX.

A limitation of this study was that the bio-switch group was a relatively small cohort. More subjects should have been assessed to evaluate the efficacy of ADA on bio-switched patients, but the experience of early LOE cases, especially those switched from ETN, made it difficult for us to increase the number of similar cases in clinical practice. However, this disadvantage does not affect the outcomes of the bio-naïve group, which are the primary objects of this study.

Conclusion

The ADA administration in the bio-naïve RA patients for 2 yeares demonstrated that the drug retention rate was high, with a rate of 79% at one year and 63% at 2 years, and remission was achieved and maintained in almost half of the cases. In the X-ray observations after 2 years of treatment, no progression of the joint destruction was seen, and some local repair of bone erosions was observed. The combination of ADA and MTX should be considered as the first choice biologic treatment in bio-naïve RA patients. In the bio-switch group, however, the ADA retention rate was low and especially switching from ETN to ADA led to poor responses. But in cases who were switched due to secondary failure of IFX, a good response was shown, so ADA can be considered as a choice for patients switching from IFX.

Conflict of interest None.

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（和文抄録）

関節リウマチのバイオナイーブおよびスイッチ症例に対するアダリムマブの使用成績

―実地臨床における2年成績―

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【はじめに】完全ヒト型抗TNF-αモノクローナル抗体のアダリムマブ（ADA）は皮下注射製剤で，外来治療が可能である．本研究では，関節リウマチ（RA）に対するADAの2年間の使用成績をバイオナイーブ例および他バイオ製剤からのスイッチ例で評価し，成績と適応について検討した．
【対象と方法】当科で2009年～2011年にRAへADAを開始した連続21症例に関し，バイオナイーブ14例（男性2例，女性12例，平均53歳，罹病期間8年，メトトレキサートMTX併用85%，平均6.6mg）とスイッチ7例（全例女性，平均67歳，罹病期間14年，MTX併用71%，平均5.7mg）での治療継続率・効果・安全性を検討した．またX線で関節破壊の進行を評価した．
【結果】バイオナイーブ例では12，24ヶ月での継続率は79%，63%と良好で，疾患活動性DAS28-ESRは平均5.2から2.6へと改善し（$p < 0.01$），約50%の症例で12ヶ月時に寛解が得られ，24ヶ月時まで維持された．アメリカリウマチ学会（ACR）50/70反応率は12ヶ月時77%で達成され，24カ月時57%で維持された．X線では骨びらん・関節裂隙狭小化ともに進行の抑制が得られた．一方，スイッチ例ではインフリキシマブ二次無効から変更した2例のみ治療効果が得られて2年間継続しえたが，それ以外は効果不十分例が多く，12カ月以降の継続率は29%と低かった．帯状疱疹による入院を21例中2例で必要とした他，注射部位反応による中止が1例生じた．
【結論】ADAはバイオナイーブでMTX併用のRAが最も良い適応で，1st choiceバイオ製剤としての疾患活動性の抑制や寛解の導入・維持，関節破壊の防止に有用である一方，他剤からのスイッチとしての選択は，より慎重にすべきと考えられた．