Short communication

Long-term follow-up of adalimumab mono-therapy for rheumatoid arthritis in Japanese patients: a report of six cases

Kunihiro Ichinose, Tomoki Origuchi*, Shin-ya Kawashiri, Naoki Iwamoto, Keita Fujikawa, Toshiyuki Aramaki, Makoto Kamachi, Kazuhiko Arima, Mami Tamai, Hideki Nakamura, Hiroaki Ida, Atsushi Kawakami, and Katsumi Eguchi

*Department of Rheumatology, Unit of Translational Medicine and *Department of Physical Therapy, Unit of Rehabilitation, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan*

Address for Correspondence:
Kunihiro Ichinose, M.D., Ph.D.
Department of Rheumatology, Unit of Translational Medicine,
Graduate School of Biomedical Sciences,
Nagasaki University, Nagasaki, Japan
1-7-1 Sakamoto, Nagasaki 852-8501, Japan
TEL: +81-95-819-7266
FAX: +81-95-849-7270
E-mail:kunizo1234abcd@yahoo.co.jp

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Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by progressive inflammatory synovitis and erosion of articular cartilage and marginal bone that generally begins early in the disease course [1]. Although the pathophysiology of RA is not well understood, the proinflammatory cytokine Tumor Necrosis Factor (TNF) -α plays an important role in the pathogenesis of RA, and it is a prime target for directed biologic agents [2]. Two TNF inhibitors, infliximab [3] (75% human and 25% mouse peptide sequences, monoclonal antibody to TNF-α) and etanercept [4] (a recombinant, human, TNF receptor-Fc fusion protein), were already commercially available. The first fully human (100% human peptide sequences) therapeutic monoclonal antibody that blocks TNF-α, adalimumab (D2E7; Abbott Laboratories, Abbott Park, IL), was approved for use and has been extensively studied in clinical trials for treatment of RA [5]. To date, study authors have reported the short-term efficacy of adalimumab in patients with RA. In Japan, adalimumab was approved to be used for RA patients in 2007, and the efficacy and safety were reported by Miyasaka et al [6]. However, there has been no report about the long-term efficacy of adalimumab for Japanese RA patients. The objectives of this study were to assess the sustained efficacy of adalimumab in long-term monotherapy for Japanese patients, and to evaluate the long-term safety and tolerability of adalimumab given subcutaneously. This is the first report of the long-term follow-up data (220 weeks) of six RA cases treated with adalimumab monotherapy in Japan.

This study was a multicenter, open trial of adalimumab given as monotherapy performed from October 2002 through April 2008. We treated 6 patients with RA, each of whom fulfilled the 1987 revised American College of Rheumatology (ACR) criteria [7] for 3 months or more, and had ≥12 tender joints and ≥ 10 swollen joints (excluding distal interphalangeal joints). They also had a C-reactive protein (CRP) concentration ≥ 2 mg/dl and a Disease Activity Score 28 (DAS28) ≥ 3.2, despite receiving standard anti-rheumatic treatment including at least one conventional Disease Modifying Anti-Rheumatic Drug (DMARD). Prior therapy with DMARD was discontinued at least 28 days before entry in the present study and returned for baseline visit within 42 days. The patients who were treated with biologic agents, including anti-CD4 antibody, within 6 months or prior treatment with any TNF antagonist or an alkylating agent were excluded. They gave their informed consent to the protocol, which was approved by the Institutional Review Board of Nagasaki University.

Table 1 summarizes the profiles of the 6 RA patients. None of the patients had received prior therapy with biologic agents. Patients were injected adalimumab by a physician at 20, 40, or 80 mg subcutaneously every other week for 220 weeks. Patients stopped taking current anti-rheumatic therapy, including any DMARDs, 28 days before starting this treatment. They were allowed to continue glucocorticoids (prednisolone equivalent ≤ 10 mg/day) and non-steroidal anti-inflammatory drugs, provided that the dosage regimens were stable from 28 days before starting the treatment to the end of the treatment. If the treatment was not effective, the doses of adalimumab were increased (cases 1 and 2: 20 mg to 40 mg at week 22, case 6: 40 mg to 80 mg at week 16). In case

5, the dose was decreased from 80 mg to 40 mg at week 22 because of the good response.

The effectiveness of adalimumab for 6 cases of RA patients was assessed at weeks 4, 16, and 28, and every 12 weeks in the extension phase using tender joint counts (TJC), swollen joint counts (SJC), visual analog scale (VAS) score, C-reactive protein (CRP) and DAS28-CRP (calculated using CRP concentration and evaluation of 28 joints) (Fig. 1). All 6 patients were women, and the median age was 54.0 ± 7.07 years old. The median duration of the disease was 7.43 ± 11.1 years, and the median score of DAS28-CRP at entry was 5.35 ± 0.69. Three patients were able to continue receiving adalimumab monotherapy for 220 weeks successfully. The median score on DAS28-CRP became 3.52 ± 1.61 at week 24, 2.79 ± 1.15 at week 48, and had decreased to 1.89 ± 0.75 by week 220. All three patients who could continue this treatment for 220 weeks showed a response for 220 weeks and achieved clinical low disease activity (DAS28-CRP<2.7).

Two patients withdrew because of lack of efficacy (case 1 discontinued at week 46; case 6 discontinued at week 48), and one patient withdrew because of adverse events (case 5 discontinued at week 88 because of non-Hodgkin lymphoma) (Table 2).

We report the effectiveness of adalimumab mono-therapy for 6 Japanese RA patients followed up for 220 weeks. In this study we found its effectiveness last long time even in 220 weeks. The efficacy and safety of adalimumab as mono-therapy in 544 RA patients for 26 weeks were previously reported. In the previous study, patients were treated with mono-therapy of adalimumab 20 mg every other week, 20 mg weekly, 40 mg every other week, or 40 mg weekly, or with a placebo. After 26 weeks, patients

were treated with adalimumab 40 mg every other week or 40 mg weekly. The groups achieved ACR20 in 46% and 53.4% of patients, respectively. These response rates were significantly better than that in the placebo group (19.1%) [8]. Recently Miyasaka et al reported that in the Clinical investigation in Highly disease-affected rheumatoid Arthritis patients in Japan with Adalimumab applying staNdard and General Evaluation (CHANGE) study, adalimumab 20, 40, and 80 mg were safe and effective in Japanese patients. All adalimumab treatment groups achieved statistically significantly higher ACR20 responses (28.7% in the 20 mg group, 44.0% in the 40 mg group, and 50.6% in the 80 mg group) compared with the placebo group (13.8%) during 24-week follow-up [6]. In our patients the median score of DAS28-CRP was decreased from 5.35 ± 0.69 to 3.52 ± 1.61 at week 24. Afterwards the efficacy continued, and the median score on DAS28-CRP had decreased to 1.89 ± 0.75 by week 220. We demonstrated 220 week long-term follow up data about the efficacy of adalimumab mono-therapy for the first time in Japan. The efficacies at week 220 were better than those at week 24. Four of 6 patients achieved DAS28<2.7, meaning clinical low disease activity at 4 weeks after starting treatment in case 2, at 16 weeks in case 3, and at 64 weeks in case 4 and case 5. Three patients continued this treatment under remission state until week 220; one patient (case 5) discontinued the treatment because of suffering from non-Hodgkin lymphoma.

The Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Rheumatoid Arthritis (ARMADA) trial [9], a 6-month, placebo-controlled, phase II/III study, demonstrated significant reductions in signs and symptoms of RA, and improvement in physical function in response to combined therapy with MTX and adalimumab. In their study, the clinical response and remission were sustained in

patients with RA during 4 years of treatment with adalimumab [10]. Although our patients were not treated with MTX, 3 patients showed a good response to adalimumab mono-therapy. Three patients were discontinued because of an adverse event in one and no response in two. One (case 6) of two non-responder patients was anti-adalimumab antibody (AAA) positive. Bartelds et al reported that lack of response to adalimumab is probably caused by the formation of AAA [11]. AAA normally appears at low levels but at high frequency, especially in Japanese RA patients.

Regarding adverse events, 2 of 6 patients (33%) experienced injection site reaction, and 2 of 6 patients had infectious adverse events, including nasopharyngitis and common colds (33%). Although the number of patients was small in our study, the occurrence of injection site reaction and infectious adverse events were almost the same as in a previous report [6], even during a 220-week follow-up. We did not experience tuberculosis or opportunistic infections. There were no reports of tuberculosis in the adalimumab treatment groups in the 24 week follow up CHANGE study in Japan [6], but there was a 4- to 7-fold increased risk of reactivation of latent tuberculosis in patients using TNF inhibitors [12, 13]. Case 5 was forced to discontinue treatment because of non-Hodgkin lymphoma in week 88. Recent reports have suggested a slight increase in the risk of lymphoma, particularly in patients with RA [14]. In the CHANGE study malignancies were reported in two patients only in the placebo group during the double-blind period. On the other hand, a recent metanalysis involving infliximab and adalimumab demonstrated an increased risk of lymphoproliferative disease and malignancies in patients treated with these agents [15]. Therefore, we have to consider both the risk and the benefit when we use TNF antagonists for RA patients.

In conclusion, among patients with RA for whom previous anti-rheumatic treatment had failed, adalimumab mono-therapy achieved significant and sustained improvements in disease activity for a long time and improved physical function while being safe and well tolerated. Our study has a limitation, because the number of patients is small. Next, we plan to increase the number of patients and examine when these patients should discontinue the treatment, which needs further investigation.

Abbreviations

RA: Rheumatoid arthritis, DAS28-CRP: the 28 joint count Disease Activity Score using C reactive protein, CRP: C-reactive protein, TNF-α:Tumor necrosis factor alpha, ACR: American College of Rheumatology, DMARD: Disease Modifying Anti-Rheumatic Drug, CHANGE: Clinical investigation in Highly disease-affected rheumatoid Arthritis patients in Japan with Adalimumab applying staNdard and General Evaluation, VAS: visual analog scale, mHAQ: modified Health Assessment Questionnaire RATIO: the French Research Axed on Tolerance of Biotherapies, ARMADA: Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Rheumatoid Arthritis, AAA: anti-adalimumab antibody

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Conflict of interest statement

None.

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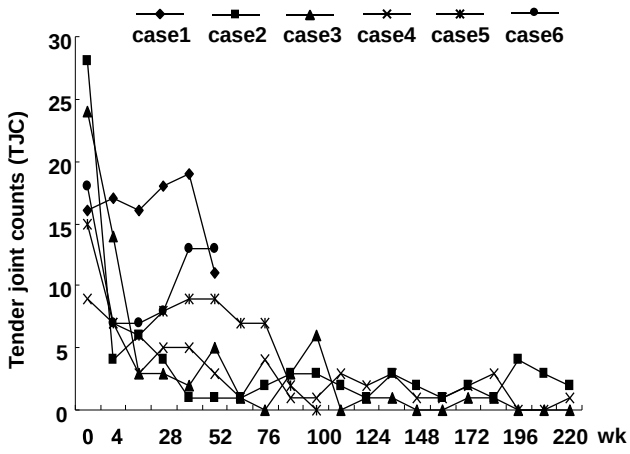
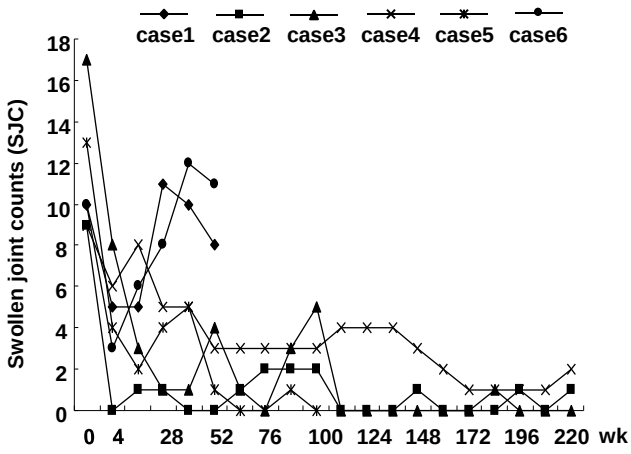
Figure Legends

Figure1. Effectiveness of adalimumab for 6 RA patients was assessed at 4, 16, and 28 weeks and every 12 weeks in the extension phase using tender joint counts (TJC), swollen joint counts (SJC), the visual analogue scale (VAS), C-reactive protein (CRP) level, and DAS28-CRP (calculated using CRP concentration and evaluation of 28 joints).


case1 case2 case3 case4 case5 case6
Tender joint counts (TJC)
0 5 10 15 20 25 30
0 4 28 52 76 100 124 148 172 196 220 wk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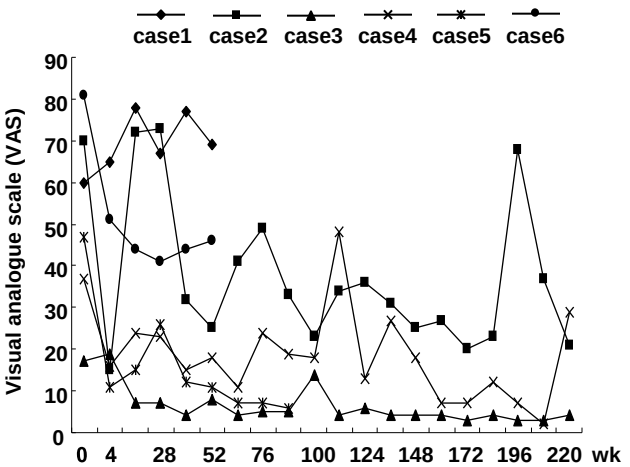
Swollen joint counts (SJC)
0 2 4 6 8 10 12 14 16 18
0 4 28 52 76 100 124 148 172 196 220 wk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Visual analogue scale (VAS)
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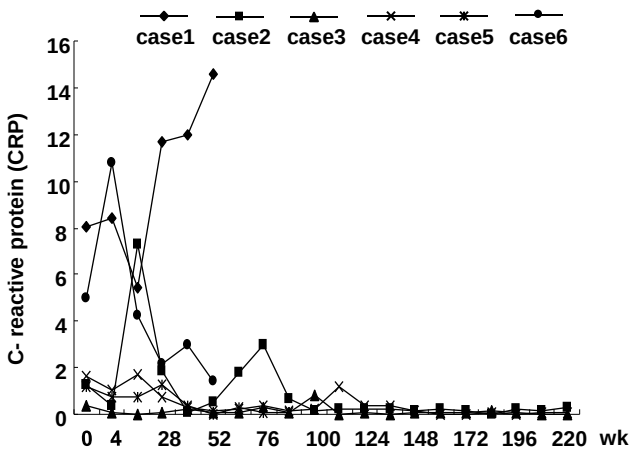
0 4 28 52 76 100 124 148 172 196 220 wk


case1 case2 case3 case4 case5 case6
C- reactive protein (CRP)
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0 4 28 52 76 100 124 148 172 196 220 wk

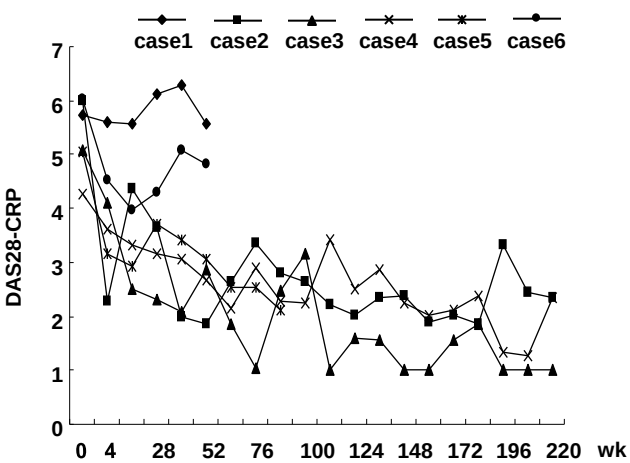
case1 case2 case3 case4 case5 case6
DAS28-CRP
0 1 2 3 4 5 6 7
0 4 28 52 76 100 124 148 172 196 220 wk

Figure 1

Case	1	2	3	4	5	6	Mean±SD
Age	53	53	52	42	58	56	54.0 ± 7.07
Sex	F	F	F	F	F	F	
BW	54.7	56	62.4	48	60.4	59.3	56.8 ± 5.16
Disease duration (years)	1.6	29.4	8	1.9	0.7	3	7.43 ± 11.1
Number of DMARDs	2	1	2	2	1	1	1.50 ± 0.55
Prednisone (mg/day)	5	5	6	5	4	4	4.83 ± 0.75
TJC	16	28	24	9	15	18	18.3 ± 6.77
SJC	10	9	17	9	13	10	11.3 ± 3.14
CRP (mg/dl)	8.02	1.25	0.38	1.63	1.21	4.96	2.91 ± 2.97
VAS (mm)	60	70	17	37	47	81	52.0 ± 23.3
mHAQ	2.25	2	1	0.5	0.5	0.875	1.19 ± 0.76
Duration of morning stiffness (min)	90	120	60	0	0	0	45.0 ± 52.8
DAS28-CRP	5.72	5.99	5.09	4.25	5.05	6.01	5.35 ± 0.69
Rheumatoid factor (IU/ml)	5	161	40	42	16	18	47.0 ± 57.7

Table 1. Demographic and clinical characteristics of 6 rheumatoid arthritis (RA) patients, F: Female. BW: body weght, DMARDs: disease modifying anti-rheumatic drugs, TJC: tender joint count, SJC: swollen joint count, CRP: C-reactive protein, VAS: visual analog scale, mHAQ: modified Health Assessment Questionnaire, DAS28-CRP: the 28 joint count Disease Activity Score using C-reactive protein.

Case	1	2	3	4	5	6
Dose (mg)	20-40	20-40	40	40	40-80	40-80
Course	discontinued	ongoing	ongoing	ongoing	discontinued	discontinued
DAS28-CRP						
Before	5.72	5.99	5.09	4.25	5.05	6.01
(treatment)	(46 wk)	(220 wk)	(220 wk)	(220 wk)	(88 wk)	(48 wk)
After	5.58	2.33	1.02	2.33	2.11	4.78
AAA	negative	negative	negative	negative	negative	positive
Adverse event	none	naso-pharyngitis	common cold	injection site reaction	non-Hodgkin lymphoma	injection site reaction

Table 2. Clinical course and response of 6 RA patients during a 220-week follow-up. DAS28-CRP: the 28 joint count Disease Activity Score using C-reactive protein, AAA: anti-adalimumab antibody