Clinical effects of half- and full-dose abatacept are equivalent

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Abstract

Objectives: To compare the clinical effect and cost effectiveness of half- and full-dosage abatacept in patients aged over 65 years diagnosed with rheumatoid arthritis.

Methods: Sixty-three elderly patients aged > 65 years with rheumatoid with abatacept were enrolled from four hospitals. Disease Activity Score using C-reactive protein (DAS 28-CRP) were evaluated as well as blood, urine, and radiographic analyses before and 52 weeks after abatacept administration.

Results: DAS 28-CRP decreased from 5.1 ± 0.9 to 2.6 ± 1.0 for half-dosage and from 4.6 ± 1.3 to 2.8 ± 0.9 for full-dosage abatacept, but the differences were not significant. Clinical improvement using DAS 28-CRP was similar in patients aged 65-74 years and those aged > 75 years.

Conclusions: Half-dosage abatacept exhibited the same clinical effect and cost effectiveness of full-dosage of abatacept. And age was not a risk factor for ABT treatment.

Key words: Abatacept, Aged, Clinical equivalence, Half-dose, Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) has been investigated as a systematic immunological disorders accompanied by inflammatory cytokine network disruption[1]. Pyramidal treatment was initiated by Smyth[2], and it consists of broad and mild to active and strong agents such as steroids. This principle aimed to diminish the side-effects of pharmacologically strong agents. In the 1990s, methotrexate (MTX) was introduced for RA treatment, resulting in an increased life span[3]. Furthermore, the introduction of biological products has had a large impact on RA treatment, making a new paradigm shift for RA treatment[4]. Namely, biological products prescribed at the early stage of RA treatment result in complete cure and biological products may be used to repair joint destruction[5]. In fact, we previously repaired the cartilage of a 27 year-old woman with RA by using biological products[6]. Biological products have been used to cure and decrease the need for surgical treatment for RA in many countries[7].

Recent clinical evidence-based developments in clinical medicine, including those for RA, have been accompanied by the development of treatment guideline[8]. Such guidelines are renewed every year or two. The latest guideline identifies biological products as the first-line treatment includes abatacept (ABT), tocilizumab, and tumor necrosis factor-α (TNF-α) inhibitors[9].

Japan is rapidly aging country, where female is the 1st, and the male is 3rd in the aged of life-span in the world ranking[10]. However, there are serious problems for such aged persons, one of which is body locomotive dysfunction. The so-called healthy life-span is minus 7-8 years in Japan. Especially in elderly persons with RA living longer, their locomotive activity may be easily impaired. Such patients may also experience cognitive declines and depression, both of which may significantly decrease their quality of life (QOL).

The administration of biological products to elderly patients with RA may cure and bring back active locomotive daily life[11]. However, biological products are very costly, and some patients with RA cannot afford them. Furthermore, the chief complaints of patients with RA are pain and psychological problem, and once pain is relieved by biological products, the patients stop visiting the clinical or discontinue their use[12]. It is clearly said that adherence of chronic pain-killers to RA patients is closely related with intolerance of alcohol[13]. As habitual alcohol intake is rather low in Japan (70th in the world ranking)[14], long-term use of chronic pain-killers has been encountered with rather difficulty.

In our previous study, RA patients administered etanercept (ETN) and in quiet stage can reduce the dosage of ETN[15]. The shorter duration of RA can reduce the dosage more. Non-TNF-α inhibitors do not require concomitant usage of MTX: furthermore, biological products are safe and convenient for elderly patients with RA. In particular, ABT, as a T-cell selective co-stimulant regulator, is considered effective at doses of 2-10mg/kg. As reported by the GO-FORWORD trial, according to the American College of Rheumatology (ACR), the number needed to treat to benefit one person (NNTB) for ACR 20 improvement was 3.1-3.6, data that are superior to the NNTB for golimumab + (4.3-4.6)[16]. Moreover, ABT did not show an increased infection risk[17]. Thus, we assume ABT is advantageous for Japanese patients, who tend to have a rather low body weight and require an increased MTX dosage. Furthermore, the government permitted changes in ABT dosage. Some agents at only half-dosage are effective in Japanese patients, as

prescribed in the United Status or in European countries. Biological products are not commonly prescribed for elderly patients with RA, owing to economic issues. In the present study, half-dose ABT was prescribed to RA patients aged > 65 years to evaluate whether it exhibits the same clinical effect of full-dosage ABT.

Materials and Methods

This clinical study included RA patients (age, 65-90 years: average, 72.7 ± 6.4 years: 10 men, 53 women). The mean disease duration was 9.9 ± 10.3 years (range, 1-50 years). Nine patients was stage Ⅰ, 14 had stage Ⅱ, 11 had stage Ⅲ, and 29 had stage Ⅳ, respectively. Patients were classified as follows: class Ⅰ, 18, class Ⅱ, 33;, class Ⅲ, 9; and class Ⅳ, 3 patients, respectively. The mean patient height was 153 ± 68.9 cm (range, 135-179 cm), while the mean body weight was 53 ± 10.5 kg (range, 35-79 kg). The mean body mass index was 21.93 ± 3.2 (range, 15.4-31.2). Of the patients cohort, 38 (60%) had never received treatment with biological agents, while 25 (40%) had shown failure to previous treatment with biological agents. There were 50 cases of osteoporosis treated by bisphosphonate + vitamin D (n-37), teriparatide (n=8), and selective estrogen receptor modulator (n=5). Other complications: 18 hypertension, 17 gastrointestinal symptoms, diabetic diseases, 6 renal dysfunctions, 3 respiratory diseases and so on. The data of patients aged > 65 years to whom ABT was administered were retrospectively collected from four hospitals. Upon the implementation of ABT, all regimen and treatments already prescribed prior to the present study were continued. The half-dose ABT regimen was 250 mg/4 weeks (intravenously) or 125 mg/2 weeks (subcutaneously). Full-dosage ABT was 10 mg/kg body weight, which translated to 500 mg/month in most patients and 750 mg/month in a few others.

The clinical evaluation (DAS 28 + physician's visual analog score {VAS}) consisting of blood and urine analyses was performed before and 8, 12, 24, and 52 weeks after the administration of ABT. On this time, we measured the matrix metalloproteinase-3 (MMP-3: Latex turbidimetric immunoassay, Fine Chemical, Toyama, Japan) and anti-cyclic citrullinated peptide (CCP: Electrochemiluminesent immune assay, Igaku Seibusugaku Laboratory, Japan) antigen levels as special parameters for RA prognosis. The patients were allowed to continue, interrupt, or change their drugs after we explained their RA prognosis. Radiographic analysis was performed modified total Sharp score before and 52 weeks after ABT administration.

We performed a sub-study of the effects of ABT in patients 65-74 and those > 75.

Results

The patients' background characteristics are shown in Table 1. In this study, the advanced stage of RA was dominant (stages Ⅲ and Ⅳ in 40 cases, 63.5% of the total). The use of MTX, conventional disease-modifying RA drugs, and steroids was unchanged from the start to ending period when they were prescribed prior to the study start. During the study, almost half of full-dosage ABT was drop out, but half-dosage of ABT was in same number. DAS 28 CRP (TJS, SJS, VAS, and CRP), and MMP-3, and physician's VAS were significantly improved. Joint destructive analysis for modified total Sharp score did not progressed significantly during this period. Clinical improvement for ABT using DAS 28 CRP is shown in Fig. 1a. Four patients dropped out at 12 weeks: 3 of them (66-. 72-, and 65-year-old women) did not follow-up at the clinic, while a 70-year-old man changed from ABT to a JAK (Janus kinase) inhibitor. Seven patients dropped out at 24 weeks: 3 of them (69-, 73-, and 70-year-old women) dropped out for economic reasons; a 66-year-old woman and a 73-year-old man deemed their therapy ineffective and changed to other biological products; and a 77-year-old woman had a pulmonary infection and an 82-year-old woman did not follow-up at the clinic. Five patients dropped out at 52 weeks, including a 70-year-old man with diabetes mellitus and a surgical site infection, a 90-year-old woman with a pulmonary infection, a 66-year-old woman who reached ABT-free remission, and an 80-year-old woman who changed to another biological products.

Results of the half- and full-dosage groups were compared. The background characteristics of the patients enrolled in this study did not differ significantly between groups (Table 2). The clinical improvement for ABT using DAS 28 CRP was very similar between groups (Fig. 1b). Thus, half-dosage ABT had the same clinical effect as full-dosage ABT.

The 65-74-year-old and > 75-year-old groups were compared. The patients' backgrounds did not differ between groups (Table 3). The clinical improvement with ABT using DAS 28 CRP was very similar between groups (Fig. 1c). Thus, age was not a risk factor for ABT treatment.

We also used DAS 28 CRP to compare the results of the high (50/63) and low (13/63) disease activity groups. Of the former, 39 continued ABT (final dose: half in 29, full in 10; DAS 28 CRP decreased from 5.1 ± 0.9 to 2.6 ± 1.0 and; from 4.6 ± 1.3 to 2.8 ± 0.9). Of the latter, eight continued ABT (final dose: half in four, full in four; DAS 28 CRP decreased from 4.6 ± 1.3 to 2.8 ± 0.9).

The estimated glomerular filtration rate (eGFR) in the trial varied widely at 8-118 mL/min/1.73m^2 (mean, 73.0 ±23.9 mL /min/1.73m^2). Among them, 16 patients had rather mild renal dysfunction, (eGFR < 60 mL /min/1.73m^2), 15 of whom have remained on ABT without complications. Thus, ABT treatment in aged patients with RA is not accompanied by renal dysfunction-related side-effects.

We showed typical case (Fig. 2). She was an 84-

year-old (height, 156 cm; body weight, 53 kg; BMI, 21.8) with stage Ⅳ and class Ⅲ RA for > 3 years. She had a history of osteoporosis, hepatitis, chronic obstructive pulmonary disease, and gastric ulcer. She has been treated with 5-10 mg/day prednisolone (Predonine; Shionogi & Co., Ltd., Japan), 0.75 μg/day vitamin D3 (Edirol; Taisho Toyama Pharmaceutical Co., Ltd., Japan), 60 mg anti-receptor activator of NF-kB ligand antibody for 6 months (Pralia; Daiichi-Sankyou Co., Ltd., Japan), 20 mg/day proton pump inhibitor (Nexum; Astra Zeneka PLC., UK), 200 mg/day tiopronin (Tiola; Pfizer, USA), 1-2 tablets of 37.5 mg tramadol and 325 mg acetaminophen (Tramcet; Janssen Pharm., USA), and 2.5mL high-molecular weight hyaluronic acid injection for 2 weeks in both the knee joints (Suvenyl; Chugai Pharmaceutical Co., Ltd., Japan). However, her symptom of knee joint swelling persisted; therefore, 10-20 mg/week buprenorphine (Norspan tape; Hisamitsu Pharmaceutical Co., Ltd., Japan) was further prescribed. Her QOL worsened, and she eventually required a wheel-chair. At this stage, ABT 125 mg/2 weeks subcutaneous injection was started. Her DAS 28 CRP decreased from the initial value of 5.75 to 4.26 at 8 weeks, 3.49 at 12 weeks, 2.97 at 24 weeks. Then prednisolone dose was decreased to 2.5 mg/day. At 52 weeks after starting ABT, DAS 28 CRP was 2.64 and buprenorphine was changed to tramadol/acetaminophen. In addition, her clinical data improved from the initial value of MMP-3 399 ng/mL to 124 ng/mL at 12 weeks, 88 ng/mL at 24 weeks, and 89 ng/mL at 52 weeks. However, anti-CCP anti-body levels changed insignificantly from 268 ng/dL to 322 ng/dL at 52 weeks. Her QOL continues to improve and she no longer requires a wheel-chair to move short distances, for example, inside a room. No serious side-effects were observed during the study period.

Table 1: The patients' background characteristics

	Starting background	**Final background**	**P value**
Age(years)	65-90 average: 72.7±6.4	66-88 average: 73.2±6.2	NS
Gender	Male10、 Female: 53	Male：7、 Female: 40	NS
Disease duration （ｙears）	1-50 average:9.9±10.3	2-51 average:10.3±11.2	NS
Stage	Ⅰ：9、Ⅱ：14、Ⅲ：11、Ⅳ：29	Ⅰ：6、Ⅱ：11、Ⅲ：9、Ⅳ：21	NS
Class	Ⅰ：18、Ⅱ：33、Ⅲ：9、Ⅳ：3	Ⅰ：14、Ⅱ：24、Ⅲ：8、Ⅳ：1	NS
Height （cm）	135-170 average: 153.0±8.9	132-168 average: 150.6±8.4	NS
Body weight (kg)	35-79 average: 53.0±10.5	33-77 average: 49.9±9.7	NS
Body Mass Index	15.4-31.2average: 21.9±3.2	14.6-32.0average: 21.6±3.3	NS
Biological treatment	Naïve: 38（60%）、Done: 25	Naïve: 20 （60％） 、Done: 17	NS
Methotrexate （ administerd cases in this study: mg/Week, average dose)	13/63 （21％）: 6.0±2.5, range 4-10	15/47（32%）: 6.4±2.0, range 4-10	NS
Conventional DMARDs	22/63（35%）: (LEF 7、BUC 7、SASP 5、TAC 2、MZB 2)	14/47（30%）: (LEF 7、BUC 7、SASP 5、TAC 2、MZB 2)	NS
Steroid （mg）	32/63 （51％）: 4.0±1.7, range 2.5-7.5	33/47（70%）: 3.6±1.5, range 2.5-7.5	NS
Starting ABT dose	Full dose : 30 、Half dose：33	Full dose : 14 、 Half dose：33	<0.05

DAS 28 CRP	4.9±1.1, range 1.9-7.1	2.7±1.0, range 1.0-4.8	<0.01
Tender Joint Score	6.6±4.6, range 0-20	2.5±2.0, range 0-8	<0.01
Swollen Joint Score	5.7±4.3, range 0-20	1.3±1.5, range 0-4	<0.01
Patient's VAS	60.2±17.4, range 10-90	32.0±20.5, range 9-79	<0.01
CRP（mg/ｄｌ）	2.9±2.7, range 0.1-9.9	3.1±2.8, range 0.1-2.2	<0.01
MMP-3（ng/ml）	277±222, range 33-965	91±89, range 17-325	<0.01
Anti-CCP antigen（mg/dl）	270±288, range 1-1090	250±343, range 1-1350	NS
modified total Sharp score	50.2±48.8, range 6-112	53.3±44.1, range 10-120	NS
Physician's VAS	60.2±17.4, range 10-90	29.2±17.1, range 10-75	<0.01

Table 2: The background characteristics of the patients between the half- and full-dosage groups Comparison for half-dose to full-dose

	Half-dose ABT group	**Full-dose ABT group**	**P value**
Age(years)	72.8±6.3, range 65-89	72.7±5.7, range 65-90	N.S.
Methotrexate（administerd cases in this study: mg/Week, average dose)	8/33（24%）: 6.0±2.6, range 4-10	5/30（17%）: 6.0±2.0, range 4-10	N.S.
Conventional DMARDs	15/33（29%） (BUC 6、SASP 4、LEF 3、MZB 1、TAC 1)	7/30（23%）: (LEF 4、BUC 1、SASP 1、TAC 1、MZB 1)	N.S.
Steroid （mg）	19/33（58%）: 3.8±1.5, range 2.5-7.5	13/30（43%）: 4.2±1.9, range 2.5-7.5	N.S.
Starting ABT dose	250mg/4 weeks: 26 、125mg/2 weeks: 7	500-750mg/4 weeks: 25、125mg/week: 5	N.S.
DAS 28 CRP	5.1±0.9, range 3.1-6.6	4.6±1.3, range 1.9-7.1	N.S.
Tender Joint Score	7.5±4.6, range 2-20	5.6±4.5, range 0-18	N.S.
Swollen Joint Score	6.8±4.9, range 0-20	4.6±3.2, range 0-11	N.S.
Patient's VAS	59.7±14.7, range 30-86	4.6±20.5, range 10-90	N.S.
CRP（mg/ｄｌ）	3.3±2.7, range 0.1-9.3	2.6±2.8, range 0.1-9.9	N.S.
MMP-3（ng/ml）	262±214, range 33-742	294±236, range 41-965	N.S.
Anti-CCP antigen（mg/dl）	217±272, range 2-1090	339±307, range 1-1050	N.S.
modified total Sharp score	49.8±51.9, range 6-108	50.3±49.7, range 10-112	N.S.
Physician's VAS	59.3±15.0, range 30-85	54.6±23.3, range 10-90	N.S.

Table 3: The background characteristics of the patients between the 65-74-year-old and > 75-year-old groups Comparison for 65-74 vs over 75 years old

	A group: 65-74 years old	B group: over 75 years old	P value
Methotrexate （administerd cases in this study: mg/Week, average dose)	9/42（21%）: 6.4±2.2, range 4-10	6/21（29%）: 6.3±1.5, range 4-8	N.S.
Conventional DMARDs	11/42（26%） (LEF 6、BUC 3、SASP 2)	4/21（19%） (SASP 2、LEF 1、MZB 1)	N.S.
Steroid （mg）	23/42（55%）: 3.4±1.4, range 2.5-7.5	13/21（62%）: 4.0±1.6, range 2.5-7.5	N.S.
Final ABT dose	Full dose: 10、Half dose: 21	Full dose: 5、Half dose: 11	N.S.
DAS 28 CRP	2.6±1.0, range 1.0-4.8	2.8±0.9, range 1.4-4.5	N.S.
Tender Joint Score	2.4±2.1, range 0-8	2.8±1.9, range 1-6	N.S.
Swollen Joint Score	1.1±1.5, range 0-4	1.8±1.5, range 0-4	N.S.
Patient's VAS	30.5±19.6, range 9-79	35.0±23.0, range 11-74	N.S.
CRP（mg/ｄｌ）	0.5±0.4, range 0.1-1.8	0.7±0.6, range 0.1-2.2	N.S.
MMP-3（ng/ml）	107±108, range 17-327	90±83, range 32-209	N.S.
Anti-CCP antigen（mg/dl）	454±460, range 70-1350	150±173, range 1-322	N.S.
modified total Sharp score	52.3±51.6, range 10-120	53.3±52.0, range 10-112	N.S.
Physician's VAS	26.8±14.3, range 10-60	34.0±12.7, range 10-75	N.S.

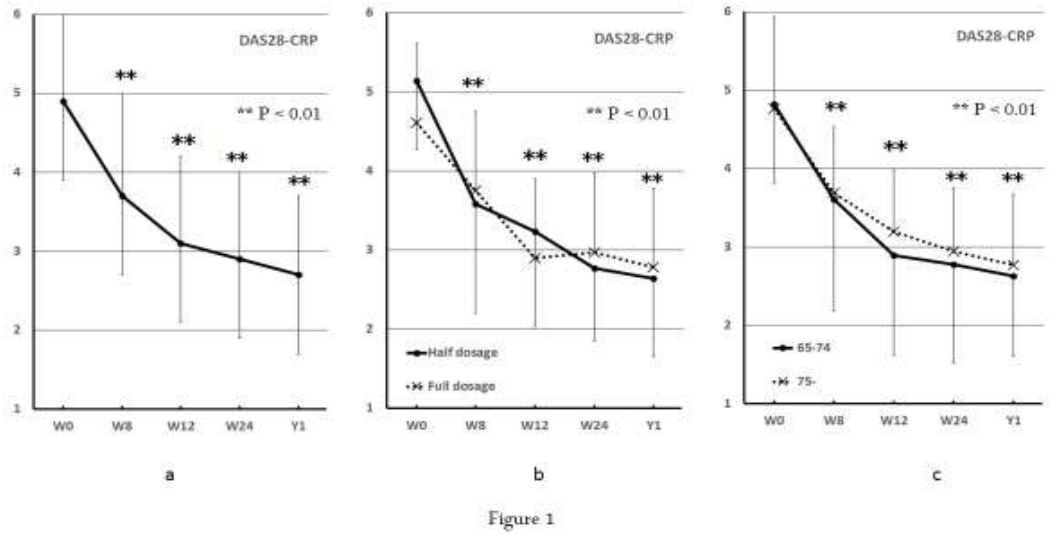

Figure 1

Fig. 1a: The clinical improvement for abatacept using DAS 28 CRP
Fig. 1b: The clinical improvement for abatacept using DAS 28 CRP between the half- and full-dosage groups
Fig. 1c: The clinical improvement for abatacept using DAS 28 CRP between the 65-74-year-old and > 75-year-old groups

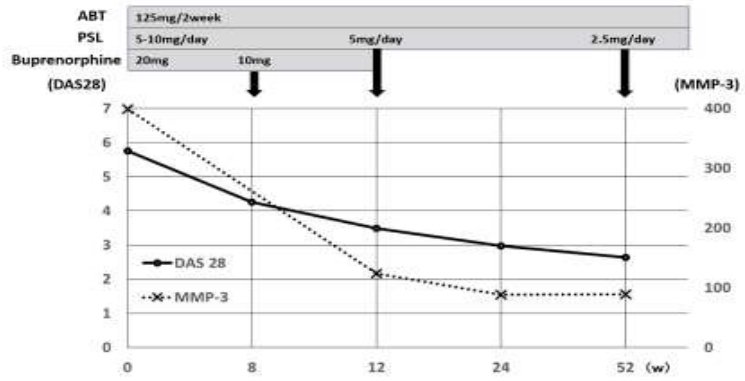

Figure 2

Fig. 2: Clinical effective prognosis of the half-dosage abatacept for 83-year-old RA woman

Discussion

To improve the destructed cartilage of elderly patients with RA, the surgical insertion of artificial cartilage may facilitate functional recovery as well as pain relief. MTX has been used for RA treatment with good effect, but in aged patients with RA, serious side effects have been reported; 583 patients died hematological disorders (32.1%), pulmonary disorders (25.9%), and infectious diseases (18.4%) between March 12, 1999 and December 31, 2014[18]. Thus, their administration to aged patients with RA, who tend to be at higher risk of side effects requires deliberate consideration. Furthermore, in patients with poor renal reserve or in those who are severely dehydrated, the RA may worsen[19].

Apart from those complicated pharmacological agents, new treatments have been developed with use of biological products such as ABT. ABT possesses several benefits for patients with RA. One of them is that its wider range of safety for various age groups, and no direct effect on renal or cardiac function[20]. However, it is related with economic issue in major handicap[21]. Therefore, the present study was designed to determine whether half-dosage ABT was as effective as full-dosage ABT for treatment of RA.

This clinical trial revealed that half-dosage ABT exhibited the same clinical efficiency as full-dosage ABT. This evidence may provide patients with RA a greater economic benefit. We have analyzed this trial further to clarify whether aged patients are at higher risk of RA treatment-related side effects. Herein, patients with RA were divided into > 75-year-old and 65-74-year-old groups. Surprisingly, we found no difference between the two groups, and ABT was safe in even super-aged patients with RA.

Japanese patients tend to be shorter and lighter, e.g. BMI is 21.9±3.2 in this study, which is very similar to that of Indian. (WHO Global Database on BMI. 2012.6.24). Asian slender patients require smaller effective doses of several pharmacological agents than American or European patients[22]. This may be because of differences in the pharmacokinetics of ABT among races; however, no clear evidence is available to explain this assumption.

These radical issue of the pharmaceutically effective dosage has been observed for several agents: the dosage of MTX is 16 mg/week in Japanese patients versus 15-25 mg/week in American/European patients; that of SASP is 1000 mg/day versus 2000 mg; that of celecoxib is 200-400 mg/day versus 400-800 mg; that of risedoronate is 2.5 mg/day versus 5 mg/day; that of rabeprazole is 10 mg/day versus 20 mg/day; and that of rosuvastatin is 2.5-20 mg/day versus 5-40 mg/day[23]. Genetic or metabolic rate differences are thought to be the cause for some agents[24]. In the present study, the kinetic data of ABT in Japanese patients were very similar to those of American/European patients[25]. Therefore, another factor may have influenced differences in ABT.

As mentioned above, the economic issue of ABT is serious for aged patients with RA: for full-dosage ABT, intravenous administration cost $917/month, subcutaneous administration cost. $932/month, respectively. Therefore, half-dosage ABT saves $460/month or $5,520/year[26]. This saving is good gospel for aged patients with RA who have limited incomes.

Concerning ABT pharmacokinetics, it is not easy to estimate plasma ABT concentrations. In addition, we found that half-dosage and full-dosage ABT have similar clinical benefits. Another study showed that 2 mg and 10 mg regimens had the same clinical effectiveness[27]. To explain those data, it is assumed that plasma ABT concentration created by half-dosage or 2 mg may

exceed Cmin. If this assumption is correct, Cmin may be >10μg/mL, a concentration that was observed in vitro to suppress T cell production[28]. The manufacturer of ABT reported that the subcutaneous administration of 125 mg once a weekly is as effective (per the drug package insert) as the intravenous infusion of ABT[29]. In this case, plasma concentration may also exceed Cmin because clinical improvement was observed.

Conflicts of interest: None

Abbreviations

DAS: Disease Activity Score, CRP: C-reactive protein, ABT: Abatacept, RA: Rheumatoid Arthritis, MTX: Methotrexate, TNF-α: Tumor necrosis factor-alfa, QOL: Quality of life, ETN: Etanercept, ACR: American College of Rheumatology, NNTB: Number needed to treat to benefit, VAS: Visual analog scale, MMP-3: Metalloproteinase-3, CCP: Cyclic citrullinated peptide, TJS: Tender joint score, SJS: Swollen joint score, JAK: Janus kinase, eGFR: estimated glomerular filtration rate.

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