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75歳以上の高齢関節リウマチ患者におけるエタネルセプトの有効性と安全性(Efficacy and safety of etanercept in rheumatoid arthritis patients over 75 years of age)

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Key words: efficacy,
elderly,
etanercept,
rheumatoid arthritis,
safety

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要　　旨

目的：近年関節リウマチ（RA）患者の高齢化に伴い高齢 RA 患者に対しても生物学的製剤を使用する機会が増えている．エタネルセプト（ETN）は血中半減期の短さから，高齢関節リウマチ（RA）

Efficacy and safety of etanercept in rheumatoid arthritis patients over 75 years of age.
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患者にも比較的安全に使用可能であると考えられ，既に多数例に使用されていると思われるが，その使用成績の報告は少ない．我々は75歳以上でETNを開始した高齢RA患者48名におけるETNの有効性と安全性を検討した．
対象・方法：2008年5月から2014年3月に当院でETNを導入した336人のRA患者のうち，導入時の年齢が75歳以上であった48例（男性18例，女性30例）を対象に，24か月を最終評価時として，患者背景，疾患活動性の推移，有害事象をretrospectiveに解析した．
結果：患者の平均年齢は79.0±2.9歳で，ETN使用により関節所見，血清学的所見，疾患活動性スコアはいずれも有意に改善を認め，使用前に比べ最終評価時ではプレドニゾロン（PSL）の平均使用量も有意に少なかった．有害事象は11例に認め，7例でETNの使用が中止され，そのうち4例は感染症であった．結核（85歳），ニューモシスチス肺炎（80歳）による死亡を各1例ずつ認めた．
結論：75歳以上の高齢RA患者において，ETNは重篤な感染症については注意が必要であるが，有効な治療手段であると考えられた．

Introduction

Recent development of bDMARDs has largely changed the management of rheumatoid arthritis (RA) so that we can achieve tight control and improved outcomes. Despite a trend of increasing biologic use for RA, the complications in elderly RA patients such as renal dysfunction or their risk of infection often circumscribes employment of bDMARDs in their treatment. According to the database of the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort [1], which is managed by Tokyo Woman's Medical University, the proportion of the RA patients over 75 years old is 12.3% at October 2011. It might as yet be higher proportion of the RA patients over 75 years old in the countryside than capital region. Some of elderly RA patients have high disease activity thus may require aggressive therapy to obtain low disease activity along with Treating RA To Target (T2T) approach [2]. The issue to cope with both of efficacy and safety in the treatment of elderly RA patient is of importance and should be substantiated So it is important problem how we treat them, we have to substantiate into daily clinics.

Etanercept (ETN), a recombinant human soluble tumor necrosis factor receptor fusion protein, is the biologics approved in January 2005, the number of the patients who use ETN are increasing these days. Early introductions of bDMARDs in early RA patients are well documented, but there are few reports of bDMARDs use in established elderly RA patients over 75 years of age. ETN has a short half-life and is considered to be safe for elderly RA patients.

Materials and Methods

We evaluated the efficacy and safety of ETN in elderly RA patients. Out of 336 patients treated with ETN at Niigata Rheumatic Center from May 2008 to March 2014, the clinical course and data of the patients who started ETN at 75 years of age or older were analyzed. All patients were diagnosed with RA according to the 2010 ACR/EULAR classification criteria for RA [3]. Tender joint counts (TJC) and swollen joint counts (SJC), C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), matrix metalloprotease-3 (MMP-3), rheumatoid factor (RF), the Disease Activity Score for 28 joint counts based on the ESR (DAS28-ESR), the simplified disease activity index (SDAI), and major adverse events were obtained from their medical records. The efficacy and safety of ETN was evaluated at 24

months. We used GraphPad Prism version 6 for all data analyses. Except where indicated otherwise, values represent mean ± standard deviation (SD) or the number of patients or the percentage. Tests were two-sided, with a type I error set at α=0.05. The differences between the parameters (TJC, SJC, patient's visual analog scale (VAS), doctor's VAS, CRP, ESR, MMP-3, RF, DAS28-ESR, SDAI) at baseline and last observation was tested using a paired t-test. To evaluate the differences of the dosage of both methotrexate (MTX) and prednisolone (PSL) 3 months before ETN was started, when ETN was started, at the last observation, we used one-way repeated measures analysis of variance (ANOVA) test and multiple comparison test. Normality was assessed with the D'Agostino-Pearson test and equality of variance with the Bartlett test. Missing data were imputed using the last observation carried forward (LOCF) method.

Results

Forty-eight patients (18 males, 30 females) with a median age of 79.0 ± 2.9 years and a median disease duration of 7.0 ± 10.1 years were analyzed (Table 1). The median height was 148.2 ± 9.5 cm and the median weight was 46.2 ± 9.1 kg. The patients were classified by the stage and class of Steinbrocker [4] as follows: Stage Ⅰ: 4 cases, Stage Ⅱ: 8 cases, Stage Ⅲ: 14 cases, and Stage Ⅳ: 22 cases; Class Ⅰ: 0 cases, Class Ⅱ: 14 cases, Class Ⅲ: 32 cases, and Class Ⅳ: 2 cases. There were 9 cases (18.8%) who had received other bDMARDs before ETN as follows: infliximab (IFX): 2 cases, tocilizumab (TCZ): 5 cases, adalimumab (ADA): 1 case, and IFX to TCZ: 1 case. The introduction dose of ETN was as follows: 20 mg/week: 1 case, 25 mg/week: 32 cases, and 50 mg/week: 15 cases. Almost all patients who were administered ETN at a dose of 50 mg/week were injected 25 mg/time twice a week. The method of administration was as follows: self-injection: 20 cases (41.7%), by a family member: 16 cases (33.3%), by general practitioners: 10 cases (20.8%), by visiting care: 1 case (2.1%), and in hospital: 1 case (2.1%).

When they start ETN, the majority of patients (93.8%) was administered conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) concurrently as described below: MTX: 47.9%, mizoribine (MZR) (daily): 25.0%, MZR (low-dose pulse): 12.5%, salazosulfapyridine (SASP): 54.2%, bucillamine (BUC): 37.5%, tacrolimus (TAC): 18.8%, and actarit (ACT): 6.3%. The average dose of MTX 3 months before ETN was started, when ETN was started, at the last observation were 6.6 ± 2.5 mg/week, 6.6 ± 2.5 mg/week, 5.6 ± 3.2 mg/week, respectively (P=0.021, but multiple comparison test are not significantly different as follows: 3 months before vs when started, P=0.84/ 3 months before vs at the last observation, P=0.057/ when started vs at the last observation, P=0.058).

About the other csDMARDs, 17 patients added some csDMARDs, and 9 patients were decreased some csDMARDs during 3 months before ETN was started as described below: the number of the patients who were started or increased TAC, SASP, MZR, BUC were 6, 3, 5, 3, respectively. And the number of the patients who were stopped or decreased TAC, SASP, MZR, BUC, ACT were 3, 2, 2, 1, 1, respectively. During follow up period, 10 patients were added some csDMARDs, and 5 patients were decreased some csDMARDs as described below: the number of the patients who were started or increased TAC, SASP, MZR, BUC were 4, 0, 3, 3, respectively. And the number of the patients who were stopped or decreased TAC, SASP, MZR, BUC were 2, 1, 2, 0, respectively.

Table 1 Patient background

Number of patients (Male/Female)	48 (18/30)
Age (years)	79.0 ± 2.9
Disease duration (years)	7.0 ± 10.1
Stage (Ⅰ/Ⅱ/Ⅲ/Ⅳ)	4 / 8 / 14 / 22
Class (Ⅰ/Ⅱ/Ⅲ/Ⅳ)	0 / 14 / 32 / 2
Body height (cm)	148.2 ± 9.5
Body weight (kg)	46.2 ± 9.1
Serum creatinine (mg/dl)	0.71 ± 2.4
Complications (%)	total: 85.4% (41/48) Hypertension: 50.0% (24/48) Diabetes mellitus: 29.2% (14/48) Osteoporosis: 31.3% (15/48) Interstitial pneumonia: 20.8% (10/48) Amyloidosis: 4.2% (2/48)
Past use of bDMRADs (%)	18.8% (IFX:2 patients / TCZ:5 patients / ADA:1 patient / IFX→TCZ:1 patient)
Disease activity of baseline	DAS28-ESR: 5.38 ± 1.10 SDAI: 27.9 ± 11.9
Initial dosage of ETN (mg/week)	20 / 25 / 50 = 1 patient / 32 patients / 15 patients
Combination use of csDMARDs at the introduction	total: 93.8% (45/48) MTX: 47.9% (23/48), 6.5 ± 2.7 mg/week MZR: 25.0% (12/48), 150.0 ± 35.4 mg/day MZR (low dose pulse): 12.5% (6/48), 400 ± 70.7 mg/week SASP: 54.2% (26/48), 923 ± 180 mg/day BUC: 37.5% (18/48), 163.9 ± 52.2 mg/day ACT: 6.3% (3/48), 266.7 ± 47.1 mg/day TAC: 18.8% (9/48), 1.7 ± 0.5 mg/day
PSL use	97.9% (47/48), 5.8 ± 2.9 mg/day

bDMARDs: biological Disease-modifying antirheumatic drugs, IFX: infliximab, TCZ: tocilizumab, ADA: adalimumab, DAS28-ESR: the Disease Activity Score for 28 joint counts based on the ESR, SDAI: Simplified disease activity index, ETN: etanercept, csDMARDs: conventional synthetic Disease-modifying antirheumatic drugs, MTX: methotrexate, MZR: mizoribine, SASP: salazosulfapyridine, BUC: bucillamine, ACT: actarit, TAC: tacrolimus, PSL: prednisolone

Most of the patients (97.9%) were also taking PSL and the average dose 3 months before ETN was started, when ETN was started, at the last observation were 5.6 ± 3.5 mg/day, 5.8 ± 2.9 mg/day, 4.9 ± 2.4 mg/day ($P < 0.0016$, 3 months before vs when started, $P = 0.70$/ 3 months before vs at the last observation, $P = 0.037$/ when started vs at the last observation, $P = 0.0008$).

For the prevention of infections, trimethoprim-sulfamethoxazole, antituberculosis drugs and a pneumococcal vaccine was administered in 58%, 60%, and 40% of the patients, respectively. Clinical parameters such as articular findings, serum marker level, and the DAS, improved significantly (Table 2). The average of the DAS28-ESR at the baseline was 5.38 ± 1.10, indicating a HDA, which decreased to a moderate disease activity (MDA) at 3 months from baseline that was maintained for 24 months (Figure 1A). Additionally, the proportion of the stage of DAS28-ESR after administration improved (Figure 1B). The average SDAI also indicated a HDA at baseline, which decreased to a MDA at 3 months from baseline and was maintained for 24 months (Figure 2A). Additionally, the proportion of the stage of

the SDAI after administration also improved (Figure 2B). A LDA or clinical remission (CR) at the last observation period was achieved in 34% of the patients according to the DAS28-ESR and 46% of the patients according to the SDAI.

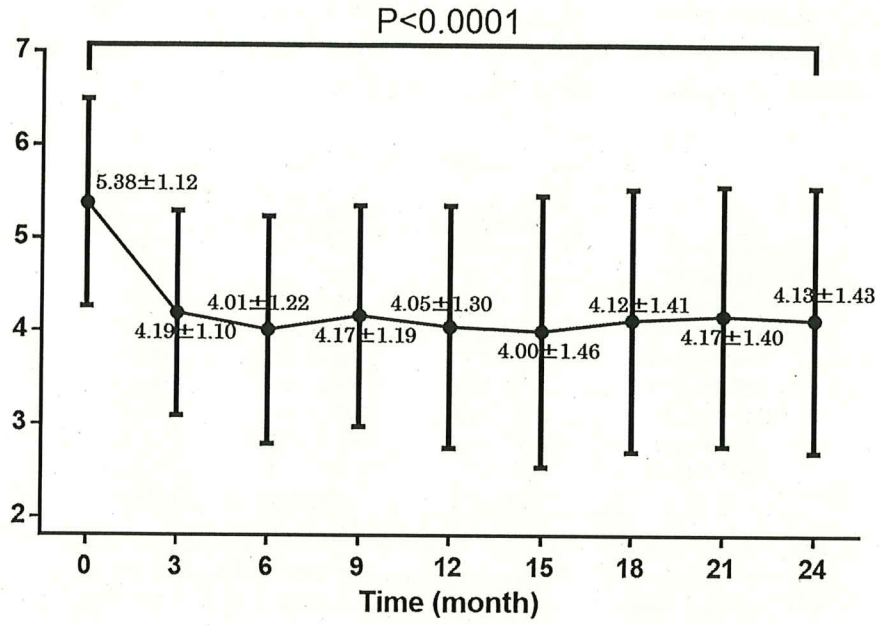
Table 2 Changes in the parameters

	Baseline	Last observation	P-Value
Tender joint count	6.1 ± 4.8	3.0 ± 3.6	P<0.01
Swollen joint count	5.1 ± 4.6	2.1 ± 2.5	P<0.01
Patient's VAS (mm)	64.1 ± 18.8	40.2 ± 27.7	P<0.01
Doctor's VAS (mm)	55.6 ± 20.2	33.1 ± 23.4	P<0.01
CRP (mg/dl)	4.2 ± 3.1	1.1 ± 1.6	P<0.01
ESR (mm/h)	55.0 ± 26.7	34.2 ± 27.4	P<0.01
MMP-3 (ng/ml)	361.6 ± 252.3	226.6 ± 141.1	P<0.01
RF (IU/ml)	185.7 ± 216.7	111.7 ± 131.6	P<0.05
DAS28-ESR	5.4 ± 1.2	4.0 ± 1.4	P<0.01
SDAI	27.0 ± 12.0	12.3 ± 9.1	P<0.01

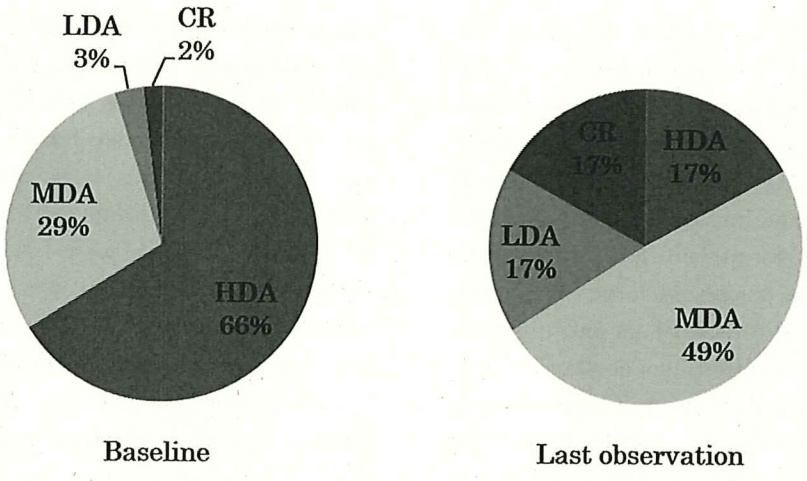
VAS: Visual analog scale, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MMP-3: Matrix metalloprotease-3, RF: Rheumatoid factor, DAS28-ESR: Disease Activity Score for 28 joint counts based on the ESR, SDAI: Simplified disease activity index

Adverse events occurred in 11 patients (Table 3). Infections occurred in 5 cases, such as tuberculosis, nontuberculous mycobacterium, pneumocystis pneumonia, urinary tract infection, and suspicion of infection. Six patients stopped ETN administration by the adverse event and 4 of these patients had infection. One patient (85 years of age) developed tuberculosis although we had prescribed an antituberculosis drug for prevention. She developed tuberculosis after finishing a year of prophylaxis in a local hospital and ultimately died due to aspiration pneumonia. When she developed it, we have used ETN 25 mg/week, MZR 150 mg/day, and PSL 7 mg/day. DAS28-ESR and SDAI were 3.17, 3.8, respectively. Another patient (80 years of age) died due to pneumocystis pneumonia (PCP); this patient was not prescribed a preventive administration of trimethoprim-sulfamethoxazole because she had a sufficient number of lymphocytes and did not exhibit any complications such as lung disease. When she developed it, we have used ETN 25 mg/week, MTX 6 mg/day, and PSL 5 mg/day. DAS28-ESR and SDAI were 4.01, 17.7, respectively. We also experienced cases of lung carcinoma, cerebral infarction, angina pectoris, toxic eruption, sub ileus and headache.

Fifteen patients out of the overall cohort changed to another bDMARDs mainly due to a loss of effectiveness, however, 28 cases (58% of all patients) have continued to receive ETN until last observation period (Figure 3) and 50% of the overall cohort have been continuing now (February 2015, the average length of using ETN was 45.4 ± 20.8 months).

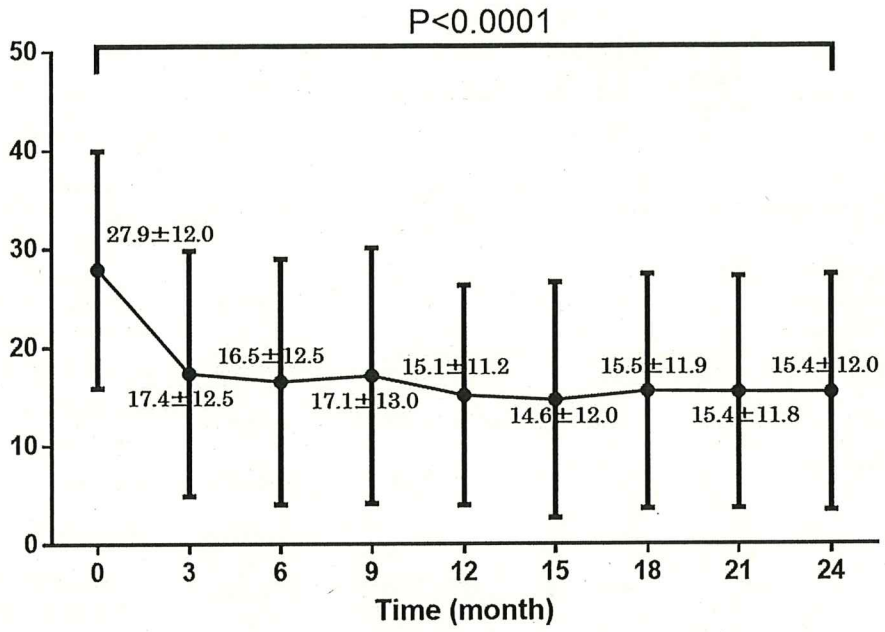


A



B

Figure 1 (A) Changes in the DAS28-ESR at every three months. (B) Disease activity by DAS28-ESR. DAS28-ESR: the Disease Activity Score for 28 joint counts based on the ESR, HDA: high disease activity, MDA: moderate disease activity, LDA: low disease activity, CR: complete remission



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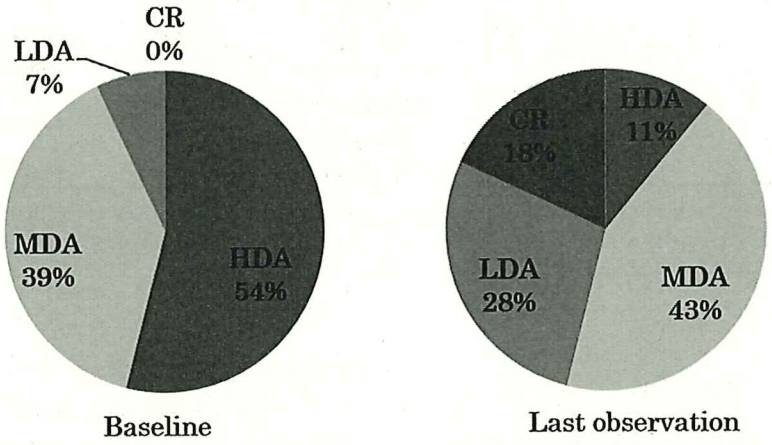

B

Figure 2 (A) Changes in the SDAI at every three months. (B) Disease activity by SDAI.
SDAI: Simplified disease activity index, HDA: high disease activity, MDA: moderate disease activity, LDA: low disease activity, CR: complete remission

Table 3 Adverse events

	Detail	Number of cases	Age at onset (yr)	Sex	Complications	Duration of ETN therapy	Outcome
Infection		5					
	Tuberculosis	1	85	F	DM Osteoporosis	18 months	stopped ETN → death by Aspiration pneumonia
	Infection caused by NTM susp.	1	81	M	HT	2 months	stopped ETN → improved → ABT → non biological DMARDs
	PCP	1	80	F	nothing	2 months	stopped ETN → death
	UTI	1	77	F	HT, IDA, LSCS	18 months	stopped ETN by the loss of effectiveness → TCZ
	Infection susp.	1	82	M	nothing	3 months	continuing ETN → GLM
Lung carcinoma		1	82	M	HT	11 months	stopped ETN → death
Cerebral infarction		1	82	M	Pneumoconiosis, IP, Osteoporosis	8 months	stopped ETN, changing hospital
Angina pectoris		1	81	F	HT, DM, IP, Osteoporosis	17 months	continuing ETN
Toxic eruption		1	80	F	HT, DM, Hypothyroidism	5 months	stopped ETN → TCZ → GLM → TCZ
Sub ileus		1	79	F	HT, DM, CRF Osteoporosis	3 months	continuing ETN
Headache		1	82	F	HT, Dyslipidemia	2 months	continuing ETN

NTM: Non tuberculous mycobacteria, PCP: Pneumocystis pneumonia, UTI: Urinary tract infection, F: Female, M: Male, DM: Diabetes mellitus, HT: Hypertension, IDA: Iron deficiency anemia, LSCS: Lumber spinal canal stenosis, IP: Interstitial pneumonia, CRF: Chronic renal failure ABT: abatacept, TCZ: tocilizumab, GLM: golimumab

Discussion

Evidence regarding the efficacy and safety of bDMARDs has been shown. However, there are few reports of biologic use in established elderly RA patients over 75 years of age. ETN has a short half-life, approximately 4 days, and is considered to be safer for elderly RA patients who are likely to develop infections compared with other bDMARDs currently available. Van Dartel et al. [5] previously reported that ETN caused less serious infection than IFX or ADA. Lurati et al. [6] administered ETN to 103 patients with RA, of which 41 patients were aged ＞65 years of age, and compared this group with a group of RA patients aged ≦65 years of age. They described that there were no differences in the rate of adverse events and ETN was safe and well tolerated by elderly RA patients. Bathon et al. [7] described the safety and efficacy of ETN in elderly (≧65 years of age) and younger adult patients (≧18 and ＜65 years of age) with RA.

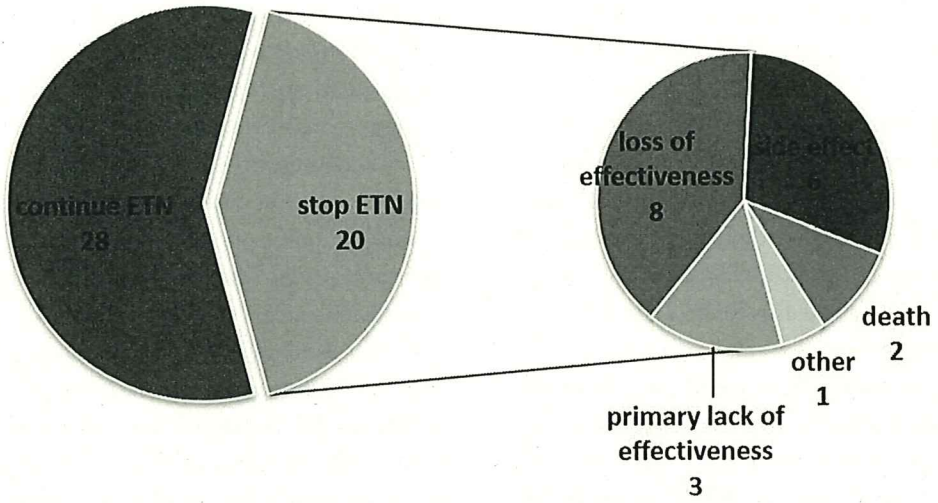

Figure 3 Outcome of the patients after ETN (at month 24)
PSL: prednisolone, TAC: tacrolimus, ADA: adalimumab, GLM: golimumab, TCZ: tocilizumab, ABT: abatacept

The authors used the data from RA patients who participated in 4 randomized, controlled clinical studies of ETN and 2 long-term observational extensions to assess whether ETN treatment was associated with a different rate of serious adverse events or serious infectious episodes in elderly versus younger RA patients. As a result of the research of 5,815 patient-years of ETN exposure, they reported that the rates of serious adverse events tended to be higher in elderly than younger patients. However, the rates of safety events observed in elderly ETN-treated subjects did not exceed the rates in elderly placebo or MTX-treated patients. Thus, the authors concluded that elderly subjects with RA treated with ETN experienced a significant improvement in the disease activity and function without incurring additional safety concerns as with younger patients. While the predominant drug currently utilized for the treatment of RA is MTX, it often induces serious side effects such as pneumonia, urinary tract infection, pancytopenia or liver dysfunction due to elevations of the blood level. Elderly RA patients in particular tend to suffer from serious side effects after being dehydrated, which occasionally result in serious outcomes. When we focus on fatal cases following MTX administration, most occurred in elderly patients over 60 years of age in Japan (Pfizer Japan Inc. Guidelines for proper use of Rheumatorex® Vol 22. URL: https://pfizerpro.jp/download.php?key=14ik2DZuAA3bERfABG5KSQ==(accessed 2017-7-5) (in Japanese)). Considering this observation, it might be safer to administer ETN for elderly patients with active RA than to administer MTX. In our study, the clinical parameters such as articular findings, serum marker level, and the disease activity score improved significantly. According to the post marketing surveillance (PMS) of ETN (Post marketing surveillance covering all patients who received ETN in Japan), the proportions of patients achieving a LDA and CR were 15.9% and 18.9%, respectively. In our study, the proportion of both LDA and CR was 17.0%, which was in agreement with that reported by

the PMS. Thus, we confirmed the efficacy of ETN for elderly RA patients over 75 years of age.

Because they often have dysfunction of the hands, there are a lot of elderly RA patients who can't inject by themselves. In that case, they can be injected by their family or general practitioner. In this study, 54.1% of elderly RA patients were injected by them and could continue using ETN.

Regarding the safety of ETN, we discontinued the administration of ETN due to serious infection in 4 cases, including 2 fatal cases. As mentioned above, one patient developed tuberculosis after the administration of an antituberculosis drug for prevention. Prophylactic chemotherapies are recommended if a patient with RA has any risk factors for tuberculosis. In Japan and many other countries, the administration of isoniazid (INH) for 6-9 months is recommended as antituberculosis chemoprophylaxis [8]. However, there are also some reports of cases which developed tuberculosis after antituberculosis chemoprophylaxis in RA patients receiving anti-TNF agents[9-13]. If there is no adverse event following antituberculosis chemoprophylaxis, then its continuation may be considered in countries with high incidences of tuberculosis, such as Japan.

In the present study, another patient died due to PCP; she was not administered a preventive administration of trimethoprim-sulfamethoxazole because she had a sufficient number of lymphocytes and did not exhibit any complications such as lung disease. Katsuyama et al. [14] identified three risk factors for PCP: at least 65 years of age, coexisting pulmonary disease, and the use of glucocorticoids. They also mentioned that RA patients with two or three risk factors for PCP receiving biologic therapy can benefit from safe primary prophylaxis. As the patient was over 65 years of age (80 years of age) and administered prednisolone (5 mg/day) in our case, we should have prescribed the preventive administration of trimethoprim-sulfamethoxazole. There were no cases of pneumococcal pneumonia in our study, however, according to the European League Against Rheumatism (EULAR) recommendations for vaccination [15], the group strongly recommends the 23-valent polysaccharide pneumococcal vaccine for patients with autoimmune inflammatory rheumatic diseases such as RA, which can induce an adequate to slightly reduced humoral response in patients with RA, even in patients treated with immunosuppressive drugs. We therefore speculate that the prevention of tuberculosis, PCP and pneumococcal pneumonia may be considered.

A limitation of this study is that there was no control group for the efficacy and safety analysis of RA patients over 75 years of age who used ETN. There was also no analysis of patients over 75 years old in the PMS (Post marketing surveillance covering all patients who received ETN in Japan). Yoshii et al. [16] reported a review of RA patients treated with bDMARDs. They reported 28 patients over 75 years old treated by bDMARDs, but only 7 patients used ETN and it is difficult to compare with our results. Also, follow up on the bone X rays was not done for every patient in our study. Further study is necessary to clarify the effect of ETN on joint destruction in elderly patients.

Although an age older than 65 years is not a risk factor for a severe infection in association with abatacept (ABT) according to the PMS of ABT, the efficacy and safety of ABT for patients older than 75 years of age remains unknown and should be studied. In addition,

among the known bDMARDs, ABT was recommended for use if patients had previous serious infections (ACR SESSIONS: New ACR Recommendations for the Management of Rheumatoid Arthritis, 2014 ACR, Boston, MA). We thus believe that it is necessary to establish evidence for cases of ETN failure or the administration of ABT as the initial bDMARDs in elderly RA patients.

Conclusion

In this study, our findings showed that ETN was an effective treatment for elderly RA patients over 75 years of age, they could decrease the disease activity of RA and the dosage of PSL without increasing MTX. Especially when we want to avoid using or increasing MTX for them by their various complications or to decrease PSL, we might consider using ETN for them. However we have to be careful of the side effects especially in serious infection, it is not yet become clear that the ETN increase additional susceptibility to infection compared with csDMARDs-treated elderly RA patients over 75 years of age. For patients who cannot perform self-injections, administration by a family member or general practitioner is effective.

Conflict of interest

Satoshi Ito received lecture fees from Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Co., Ltd., Janssen Pharmaceutical K. K., Bristol-Myers Squibb, Eisai Co., Ltd., and AbbVie. Haneda M. received research grant from Takeda Pharmaceutical Co Ltd. All other authors declare that they have no conflicts of interest.

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ABSTRACT

Efficacy and safety of etanercept in rheumatoid arthritis patients over 75 years of age

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Objectives：Introduction of biological disease-modifying antirheumatic drugs (bDMARDs) in early rheumatoid arthritis (RA) patients is well documented, however, there are few reports of biologic use in established elderly RA patients over 75 years of age. We herein evaluated the use of etanercept (ETN), which has a short half-life and considered to be safe, for elderly RA patients.

Patients and Methods：Out of 336 patients treated with ETN at Niigata Rheumatic Center from May 2008 to March 2014, the clinical course and data of the patients who started ETN at 75 years

of age or older were analyzed. The efficacy and safety of ETN was evaluated at 24 months.
Results : Forty-eight patients (18 males, 30 females) with a median age of 79.0 ± 2.9 years were analyzed. Clinical parameters such as articular findings, serum marker level, and the disease activity score improved significantly and the average dose of prednisolone (PSL) after using ETN were also decreased significantly compared with before using it. Adverse events occurred in 11 patients. Seven patients stopped ETN and 4 of these patients developed an infection. One patient (85 years of age) died due to tuberculosis and another (80 years of age) died due to pneumocystis pneumonia.
Conclusions : We may have to pay attention to the adverse event especially in the serious infection for elderly RA patients, but ETN is thought to be an effective treatment for elderly RA patients over 75 years of age.