



# Subcutaneous Tocilizumab Is Effective for Treatment of Elderly-Onset Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is an autoimmune disease characterized by systemic articular and bone manifestations and its pathogenesis is driven by a complex network of proinflammatory cytokines, including tumor necrosis factor and interleukin (IL)-6. Treatment of rheumatoid arthritis (RA) has been standardized by the introduction of a treat-to-target approach. Subcutaneous tocilizumab (TCZ-SC) is a humanized anti-IL-6 receptor monoclonal antibody, and is widely used for refractory RA patients in the clinical settings. However, it remains unknown whether TCZ-SC shows effectiveness for elderly onset RA. The study was aimed to assess the effectiveness and safety of TCZ-SC in elderly-onset rheumatoid arthritis (EORA) patients in daily practice. Fifty-five RA patients were divided into two age groups upon TCZ-SC administration: young (Y) group (< 65 years old, n = 30) and elderly-onset (EO) group (> 65 years old, n = 25). Disease activity score-28 (DAS28) upon TCZ-SC administration (4.84 in EO group vs. 4.41 in Y group) was significantly decreased to 1.94 vs. 1.93 at 3 months and 1.61 vs. 1.75 at 12 months after administration. The clinical remission (DAS28 < 2.6) rate was 75% in EO group vs. 83% in Y group at 3 months and 90% vs. 85% at 12 months. The retention rate at 12 months was 88% in EO group and 92% in Y group without significant difference. The cessation cases of adverse events were two in each group. In conclusion, TCZ-SC showed good clinical effectiveness and safety in EORA patients. TCZ-SC is a useful agent for patients with EORA.

**Keywords:** effectiveness; elderly onset rheumatoid arthritis; retention rate; safety; subcutaneous tocilizumab  
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## Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory condition with progressive and systemic inflammation resulting in joint destruction and functional disability (Willemze et al. 2012). Recently treat-to-target strategy has been widely introduced for aiming at reducing disease activity of RA and achieving remission or low disease activity within 6 months. Early intervention with methotrexate plus glucocorticoids and subsequently with other disease modifying anti-rheumatic drugs such as tumor necrosis factor inhibitors, anti-interleukin-6 (IL-6) receptor monoclonal antibody, T-cell costimulatory modulating inhibitor, and Janus kinases have been performed (Aletaha and Smolen 2018).

Tocilizumab (TCZ) is a humanized anti-IL-6 receptor monoclonal antibody that antagonizes the effects of IL-6 by

preventing its binding to its receptor (Nishimoto et al. 2007). As treatment in RA patients, TCZ induced a rapid and sustained improvement in signs and symptoms, and TCZ has some advantages in RA patients who cannot use methotrexate (MTX) and are non-responders to tumor necrosis factor (TNF) inhibitors (Ogata et al. 2012) or in patients with moderate to severe RA (Dhillon 2014).

Since 2013, subcutaneous tocilizumab (TCZ-SC) has been widely used in Japan for refractory RA patients (Nakashima et al. 2014; Atsumi et al. 2018). The proportion of elderly-onset RA (EORA) patients has recently increased (Sugihara and Harigai 2016). Japan Gerontological Society had defined that elderly people are individuals older than 65 years old. Recently, it updated the definition of elderly people as individuals older than 75 years old. EORA patients have more severe dysfunction of the renal system and other organs. In addition, EORA patients have

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other complicated comorbidities, such as hypertension, diabetes mellitus, and cardiovascular diseases (Sugihara and Harigai 2016). Thus, they tend to be treated with polypharmacy. These conditions make it difficult to treat them compared with having RA alone. Compared with young-onset RA, elderly-onset RA showed higher disease activity and higher health assessment score and higher bone erosion (Innala et al. 2014). In addition, elderly-onset RA patients have been recently increased according to a nationwide database in Japan (Kato et al. 2017).

The clear guidelines or recommendations for patients with EORA has not been estimated. Moreover, whether TCZ-SC shows effectiveness in elderly onset patients with RA is not clarified yet. Hence, this study aimed to examine the clinical outcome and compare the effectiveness and safety of TCZ-SC administration between young and elderly RA patients, using data from the Japanese multi-center registry system Niigata Orthopaedic Surgery and related facilities Rheumatoid Arthritis Database (NOSRAD).

### Patients and Methods

This observational study was approved by the Institutional Review Board (IRB) at Niigata University School of Medicine (ID number 1345) and had obtained ethical clearance. Informed consent was obtained for all enrolled patients.

NOSRAD was established to explore the prognosis of anti-rheumatic drugs such as conventional synthetic disease-modifying antirheumatic drug (DMARDs), biological DMARDs (bDMARDs), and target synthetic DMARDs in RA patients in clinical practice. It was also approved by the IRB of Niigata University School of Medicine (ID number 2019-0377). From NOSRAD, 58 RA patients were enrolled. Inclusion criteria were the age of > 17 years and refractory RA to conventional synthetic DMARDs, MTX or other biological DMARDs for more than 3 months. Exclusion criteria were the complicated case with malignant tumor and elderly RA patients above 65 years old who were not elderly onset (elderly onset was defined as above 65 years old at RA onset age). Three patients were excluded, and the remaining 55 RA patients were analyzed.

All patients fulfilled the 1987 ACR criteria (Arnett et al. 1988) or the 2010 ACR/EULAR classification criteria for RA (van der Linden et al. 2011). Patient anonymity was maintained during data collection. Written informed consent was obtained from all participants. They were divided into the following two groups. Elderly-onset RA group (All the cases' onset age was above 65 years old) and was defined as "elderly-onset (EO) group" and the cases whose TCZ-SC administration age were less than 65 years old was defined as "young (Y) group". They were prospectively followed until 12 months after TCZ-SC administration. TCZ-SC (Actemra® subcutaneous injection 162 mg autoinjector, Chugai Pharmaceuticals, Utsunomiya, Tochigi, Japan) was injected biweekly in all cases.

Self-injection rate of TCZ-SC, RA disease duration, bio-naïve rate, and previously used medications were evaluated in each group. In addition, the dose of MTX and prednisolone (PSL), anti-cyclic citrullinated peptide (anti-CCP) antibody, rheumatoid factor (RF), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), matrix metalloproteinase-3 (MMP-3), disease activity score-28 (DAS28), and clinical disease activity index (CDAI) were evaluated upon TCZ-SC administration, as well as the transition of PSL and MTX. Serum MMP-3 was analyzed by sex (man and woman) because of the difference of the reference values. To compare renal function, serum creatinine and estimated glomerular filtration rate (eGFR) were analyzed.

The transition of DAS28, DAS28 remission rate, European League Against Rheumatism (EULAR) response, CDAI, serum MMP-3, were followed at the TCZ-SC administration, 3, 6, and 12 months after the TCZ-SC administration. PSL and MTX doses were evaluated at the administration of TCZ-SC and 12 months after the TCZ-SC administration.

All data were presented as mean  $\pm$  standard deviation. Statistical analysis was performed using GraphPad Prism 6J (Tokyo, Japan). Fisher's exact test, Student's or Welch's *t*-test, and paired *t*-test were used, and  $p < 0.05$  indicated significant difference.

Cases of TCZ-SC cessation were determined and evaluated. The retention rates of TCZ-SC between EO group and Y group were compared by Log-rank test.

### Results

#### *Comparison of elderly onset and young groups at the baseline*

Demographic data of the registered patients are shown in Table 1. The self-injection rate was significantly lower in the elderly-onset (EO) group than in the young (Y) group (8% vs. 60%,  $p < 0.0001$ ). The average patient age was  $75.4 \pm 6.2$  years old in EO group and  $49.3 \pm 9.8$  years old in Y group ( $p < 0.001$ ).

No significant difference in RA duration was detected between the two groups (EO group at  $5.1 \pm 5.9$  years vs. Y group at  $6.7 \pm 9.4$  years,  $p = 0.45$ ; Table 1). The proportion of bio-naïve cases showed no significant difference: 21 patients in EO group (84%) vs. 23 patients in Y group (77%) ( $p = 0.74$ ). The remaining four patients in EO group had been treated with bDMARDs other than TCZ-SC (Table 1): abatacept (ABA) in three patients, adalimumab (ADA) in one patient, etanercept (ETN) in one patient, and intravenous tocilizumab (TCZ-IV) in one patient. Likewise, the bDMARDs used for the remaining seven patients in Y group were ETN (four patients), ADA (two patients), certolizumab pegol (CZP) (two patients), and TCZ-IV (two patients).

No significant difference was detected in the MTX doses (EO group at  $6.0 \pm 1.6$  vs. Y group at  $7.5 \pm 1.8$  mg/week,  $p = 0.15$ ), but the rate of MTX treatment in EO group was significantly lower than that in the young group (EO

Table 1. Demographic data of the elderly onset (25 cases) and young (30 cases) patients with rheumatoid arthritis.

Item	Unit	Elderly-onset (EO)	Young (Y)	p value
The number of cases	n	25	30	
Self injection	n	2	18	
Self injection rate	%	8	60	< 0.0001*
Age	Years old	75.4 ± 6.2	49.3 ± 9.8	< 0.0001*
Age range	Years old	66-84	24-63	
Women	n, %	22, 88	25, 83	
RA duration	Years	5.1 ± 5.9	6.7 ± 9.4	0.45
RA duration range	Years	0.08-19	0.08-34	
Bionaive	n	21	23	0.74
	%	84	77	
Prebiologics	n	4	7	
Details		ABA 3	ETN 4	
		ADA1	ADA 2	
		ETN 1	CZP 2	
		TCZ-IV 1	TCZ-IV 2	
MTX dose	mg/week	6.0 ± 1.6	7.5 ± 1.8	0.15
MTX cases, rate	n, %	4, 16	15, 50	0.01*
MTX range	mg/week	4.0-8.0	6.0-10	
PSL dose	mg/day	5.0 ± 0.7	5.2 ± 2.6	0.85
PSL cases, rate	n, %	9, 36	9, 30	0.77
PSL range	mg/day	5.0-10	2.5-10	
Anti-CCP antibody	IU/l	102 ± 260	113 ± 224	0.87
Anti-CCP antibody positive rate	%	47	53	0.55
RF	U/ml	107 ± 184	70 ± 72	0.32
RF positive rate	%	56	80	0.08
CRP	mg/dl	4.0 ± 4.9	2.1 ± 2.6	0.08
ESR	mm/hr	51 ± 37	33 ± 28	0.04*
MMP-3, Women	ng/ml	443 ± 619	311 ± 345	0.36
MMP-3, Men	ng/ml	168 ± 127	417 ± 369	0.4
DAS28		4.84 ± 0.98	4.41 ± 1.20	0.16
CDAI		22.4 ± 5.9	21.9 ± 7.5	0.96
Cre	mg/dl	0.65 ± 0.3	0.59 ± 0.17	0.27
eGFR	ml/min/1.73 m <sup>2</sup>	78 ± 22	95 ± 26	0.006*

Data indicate at the TCZ-SC administration in terms of MTX, PSL, anti-CCP, RF, CRP, ESR, MMP-3, DAS28, and CDAI.

ABA, abatacept; ADA, adalimumab; anti-CCP, anti-cyclic citrullinated peptide; CDAI, clinical disease activity index; Cre, creatinine; CRP, C-reactive protein; CZP, certolizumab pegol; DAS28, disease activity score 28; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; ETN, etanercept; MMP-3, matrix metalloproteinase-3; MTX, methotrexate; PSL, prednisolone; RF, rheumatoid factor; TCZ-IV, intravenous tocilizumab; TCZ-SC, subcutaneous tocilizumab.

\*p < 0.05.

group at 16% vs. Y group at 50%, p = 0.01). Neither the PSL doses (EO group at 5.0 ± 0.7 vs. Y group at 5.2 ± 2.6 mg/day, p = 0.85) nor the rate of PSL treatment (EO group at 36% vs. Y group at 30%, p = 0.77) showed significant difference (Table 1).

For anti-CCP antibody (EO group at 102 ± 260 vs. Y group at 113 ± 224 IU/l) and RF (EO group at 107 ± 184 vs. Y group at 70 ± 72 U/ml), no significant difference was observed (p = 0.87 in anti-CCP antibody and p = 0.32 in RF, respectively). In addition, there was no significant dif-

ference in the positive rate of anti-CCP antibody (EO group at 47% vs. Y group at 53%, p = 0.55) and RF (EO group at 56% vs. Y group at 80%, p = 0.08), respectively.

As regards renal function, no significant difference was detected in serum creatinine between EO and Y groups (0.65 ± 0.3 vs. 0.59 ± 0.17, p = 0.27). However, eGFR in EO group was significantly lower than that in Y group (78 ± 22 vs. 95 ± 26, p = 0.006) (Table 1).

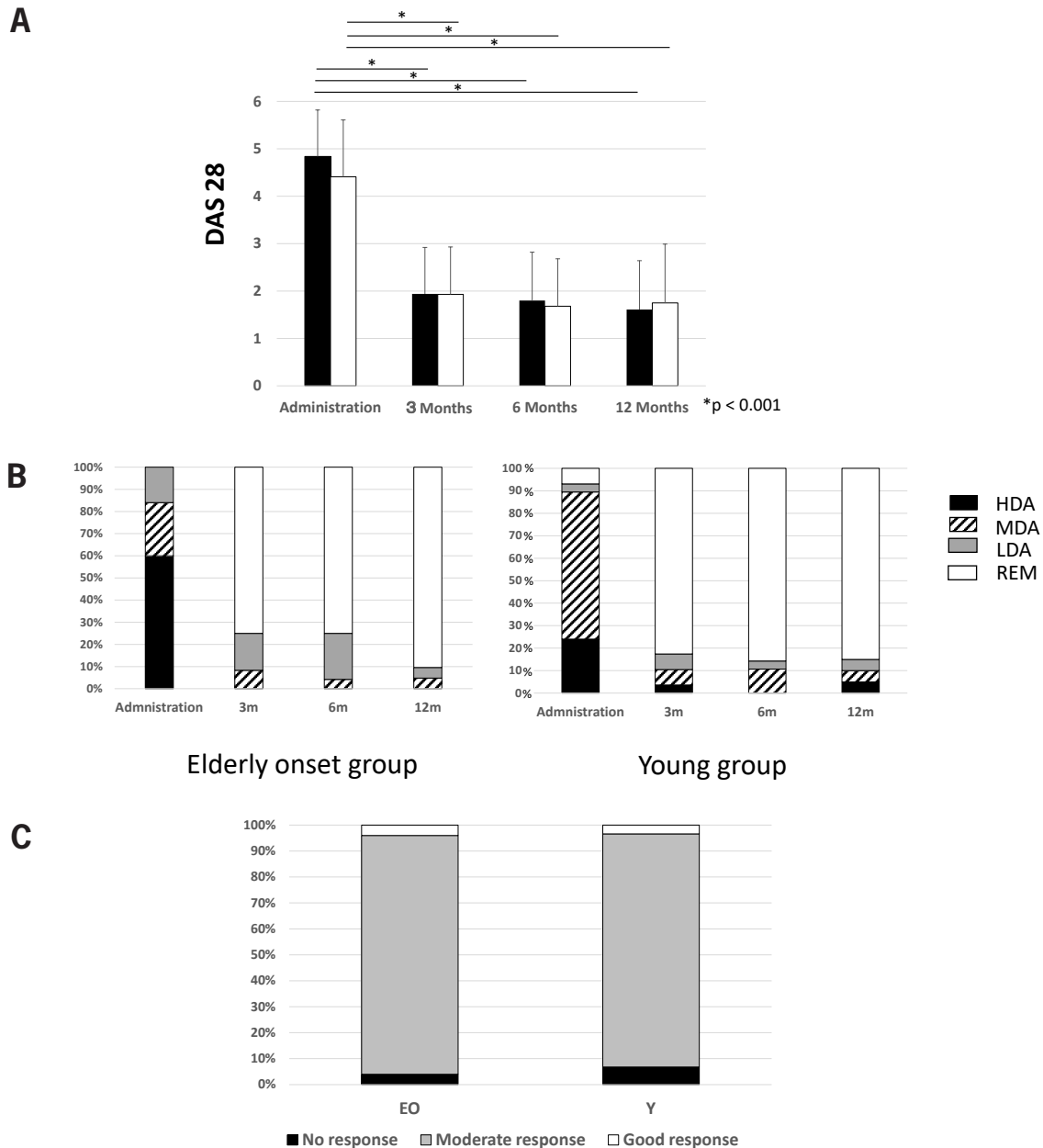


Fig. 1. The main clinical outcomes of subcutaneous tocilizumab.

(A) Disease activity score 28 transition. On administration, no significant difference was detected between the two groups (elderly onset (EO) group in 25 cases at  $4.84 \pm 0.98$  vs. young (Y) group in 30 cases at  $4.41 \pm 1.20$ ,  $p = 0.14$ ). At 3 months after subcutaneous tocilizumab (TCZ-SC) administration, both groups showed significantly low disease activity score 28 (DAS28) (EO group at  $1.94 \pm 0.98$  vs. Y group at  $1.93 \pm 1.01$ ). At 6 months, DAS28 was  $1.80 \pm 1.02$  in EO group and  $1.68 \pm 1.01$  in Y group. At 12 months after TCZ-SC administration, DAS28 was  $1.61 \pm 1.03$  in EO group and  $1.75 \pm 1.23$  in Y group. No significant difference was detected at 3, 6, and 12 months after TCZ-SC administration between the two groups.

Black bar: elderly onset (EO) group. White bar: young (Y) group.

(B) Disease activity at each time course.

In EO group, HDA (60%) and MDA (24%) were dominant at TCZ-SC administration. By contrast, at 3 months, the proportions of LDA (16.7%) and REM (75%) were dominant. At 6 and 12 months, this condition was maintained. At 12 months, the proportions of LDA (4.8%) and REM (90.4%) reached to more than 95%.

In Y group, HDA (24%) and MDA (65.5%) were dominant at TCZ-SC administration. By contrast, at 3 months, the proportions of LDA (6.9%) and REM (82.6%) were dominant. At 6 and 12 months, this condition was also maintained similar to that in EO group. At 12 months, the proportions of LDA (5%) and REM (85%) reached to 90%.

Black bar: High disease activity (HDA). Black dashed line bar: Moderate disease activity (MDA). Gray bar: low disease activity (LDA). White bar: remission (REM).

(C) EULAR response based on DAS28. Almost all cases were moderate response at the final follow up phase in both groups (92% in EO group vs. 89.8% in Y group).

### The effectiveness of TCZ-SC

CRP levels were not significantly different between EO and Y groups ( $4.0 \pm 4.9$  vs.  $2.1 \pm 2.6$  mg/dl,  $p = 0.08$ ). ESR showed significant increase in EO group compared with Y group ( $51 \pm 37$  vs.  $33 \pm 28$  mm/h,  $p = 0.04$ ) (Table 1). Moreover, serum MMP-3 levels showed no significant decrease between the two groups in women (EO group at  $443 \pm 619$  vs. Y group at  $311 \pm 345$  ng/ml,  $p = 0.36$ ) and in men (EO group at  $168 \pm 127$  vs. Y group at  $417 \pm 369$  ng/ml,  $p = 0.4$ ).

For DAS28, both groups had moderate disease activity, and no significant difference was observed (EO group at  $4.84 \pm 0.98$  vs. Y group at  $4.41 \pm 1.2$ ,  $p = 0.16$ ) (Table 1). DAS28 in the elderly onset (EO) group were  $1.94 \pm 0.98$ ,  $1.80 \pm 1.02$ , and  $1.61 \pm 1.03$ , while those in the young (Y) group were  $1.93 \pm 1.01$ ,  $1.68 \pm 1.00$ , and  $1.75 \pm 1.24$  at 3, 6, and 12 months, respectively, after TCZ-SC administration (Fig. 1A).

DAS28 at 3 months after TCZ-SC administration was significantly lower than that upon TCZ-SC administration in both groups. The proportional distribution of disease activity depending on DAS28 in each phase were shown as Fig. 1B. At the administration of TCZ-SC, clinical remission rate was 0% in EO group. And they were 75, 75, and 90.4% at 3, 6, and 12 months after TCZ-SC administration in EO group. As for Y group, it was 6.9% at the administration of TCZ-SC. Then, they were 82.6, 85.7, and 85% at

3, 6, and 12 months after TCZ-SC administration. The clinical remission rates reached more than 75% only 3 months after TCZ-SC and maintained around 90% until 12 months in both groups. About EULAR response rate, moderate response rate was highest in both groups (92% in EO group and 89.8% in Y group, respectively) (Fig. 1C).

No significant difference in CDAI was observed at TCZ-SC administration between the two groups (EO group at  $22.4 \pm 5.9$  vs. Y group at  $21.9 \pm 7.5$ ,  $p = 0.77$ ) (Table 1). CDAI in EO group were  $8.3 \pm 5.9$ ,  $6.5 \pm 5.8$ , and  $4.1 \pm 4.3$ , while those in Y group were  $7.7 \pm 5.3$ ,  $5.9 \pm 4.8$ , and  $4.8 \pm 5.2$  at 3, 6, and 12 months after TCZ-SC administration, respectively (Fig. 2).

Significant decrease in CDAI was observed in both groups at 3, 6, and 12 months compared with that in each group after TCZ-SC administration. In addition, CDAI was significantly decreased at 6 months ( $p = 0.03$ ) and 12 months ( $p = 0.013$ ) after TCZ-SC administration compared at 3 months after TCZ-SC administration in EO group. CDAI was significantly decreased at 6 months ( $p = 0.02$ ) compared at 3 months but not significantly decreased at 12 months ( $p = 0.09$ ) in Y group (Fig. 2).

In female patients in EO group, serum MMP-3 levels were  $263 \pm 470$ ,  $211 \pm 340$ , and  $131 \pm 215$  ng/ml at 3, 6, and 12 months after TCZ-SC administration, respectively. Significant difference was only detected at 12 months after TCZ-SC administration compared with that upon adminis-

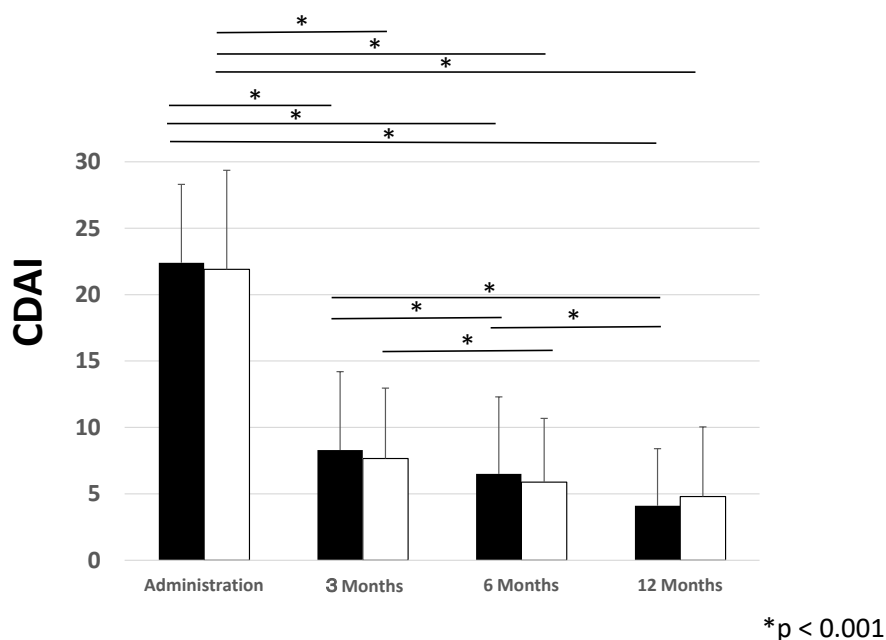


Fig. 2. Transition of the clinical disease activity index (CDAI).

On subcutaneous tocilizumab (TCZ-SC) administration, no significant difference was detected between the two groups (EO group in 25 cases at  $22.4 \pm 5.9$  vs. Y group in 30 cases at  $21.9 \pm 7.5$ ,  $p = 0.98$ ). At 3 months after TCZ-SC administration, both groups showed significant decrease in clinical disease activity index (CDAI) compared with those upon TCZ-SC administration (EO group at  $8.3 \pm 5.9$  vs. Y group at  $7.7 \pm 5.3$ ,  $p < 0.001$ ). At 6 months, CDAI were  $6.5 \pm 5.8$  in EO group and  $5.8 \pm 4.8$  in Y group. At 12 months after TCZ-SC administration, CDAI was  $4.1 \pm 4.3$  in EO group and  $4.8 \pm 5.2$  in Y group, respectively. No significant difference at 3, 6, and 12 months after TCZ-SC administration was detected between the two groups.

Black bar: elderly onset (EO) group. White bar: young (Y) group

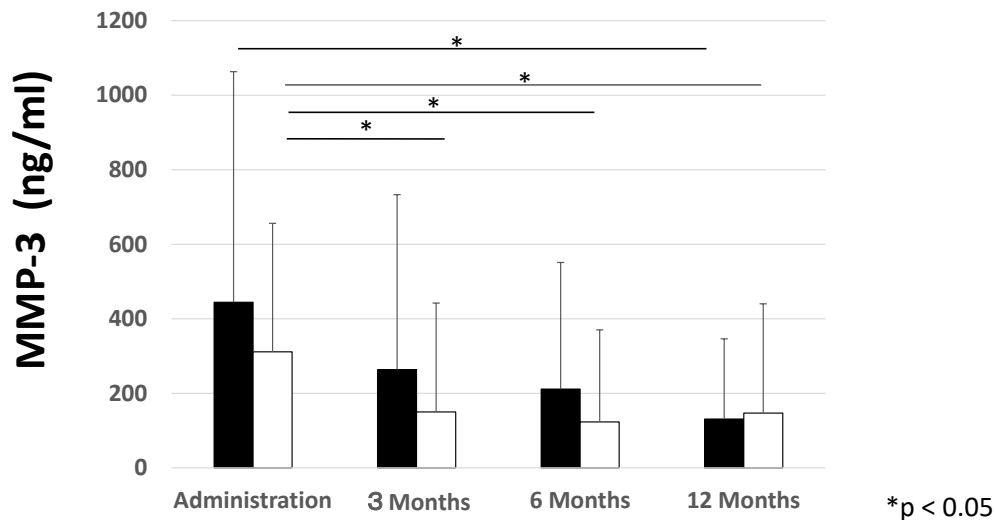


Fig. 3. Serum matrix metalloproteinase-3 transition in women cases.

On administration, no significant difference was detected between the two groups (EO group at  $443 \pm 619$  vs. Y group at  $311 \pm 344$  ng/ml,  $p = 0.36$ ). No significant difference was observed between the two groups at 3, 6, and 12 months. In EO group (22 cases), serum matrix metalloproteinase-3 (MMP-3) levels were  $263 \pm 470$ ,  $211 \pm 340$ , and  $131 \pm 215$  ng/ml at 3, 6, and 12 months after TCZ-SC administration, respectively. Significant difference in serum MMP-3 level at 12 months vs. upon TCZ-SC administration was detected ( $p < 0.05$ ).

In Y group (25 cases), serum MMP-3 levels were  $150 \pm 292$ ,  $123 \pm 247$ , and  $147 \pm 293$  ng/ml at 3, 6, and 12 months after TCZ-SC administration, respectively. Levels of serum MMP-3 at 3, 6, and 12 months after TCZ-SC showed significant decreases compared with serum MMP-3 level upon TCZ-SC administration ( $p < 0.05$ ).

MMP-3, matrix metalloproteinase-3; TCZ-SC, subcutaneous tocilizumab.

Black bar: EO group. White bar: Y group.

tration ( $p = 0.02$ ). In women patients in Y group, serum MMP-3 levels were  $150 \pm 292$ ,  $123 \pm 247$ , and  $147 \pm 293$  ng/ml at 3, 6, and 12 months after TCZ-SC administration, respectively. Significant decrease was detected at 3, 6, and 12 months after TCZ-SC administration in Y group ( $p = 0.007$  at 3 months,  $p = 0.005$  at 6 months, and  $p = 0.03$  at 12 months) compared with that upon administration (Fig. 3). For serum MMP-3 levels in men, no significant decrease was detected at 3, 6, and 12 months after TCZ-SC administration in each group compared with those upon TCZ-SC administration (data not shown).

#### The transition of prednisolone and methotrexate use

The transition of PSL dose between TCZ-SC administration and the final follow-up (12 months after TCZ-SC) are shown in Fig. 4A. In EO group, the PSL daily dose was not significantly reduced from  $5.0 \pm 2.4$  mg/day upon TCZ-SC administration to  $3.2 \pm 2.0$  mg/day at 12 months after TCZ-SC administration ( $p = 0.06$ ). In Y group, the PSL daily dose was significantly reduced from  $5.2 \pm 2.6$  mg/day to  $2.3 \pm 2.0$  mg/day ( $p = 0.0049$ ) (Fig. 4A).

The transition of MTX between upon TCZ-SC administration and 12 months after TCZ-SC administration is shown in Fig. 4B. In EO group, MTX dose was not significantly reduced from  $6.0 \pm 1.6$  mg/week to  $5.5 \pm 1.9$  mg/week ( $p = 0.39$ ). In Y group, MTX dose was significantly reduced from  $7.5 \pm 1.8$  mg/week upon TCZ-SC administration to  $3.7 \pm 3.2$  mg/week at 12 months after TCZ-SC administration ( $p = 0.0015$ ).

#### Cases of TCZ-SC cessation

Four adverse events, namely, nontypical mycobacterium (in a 78-year-old female patient), drug eruption (in a 79-year-old female patient), surgical site infection (in a 59-year-old female patient), and worsening of interstitial pneumonia (in a 63-year-old male patient), occurred. For the surgical site infection, TCZ-SC was withdrawn 2 weeks before the primary surgery. Then, tenosynovectomy of the flexor digitorum and pollicis tendons and median nerve release were performed. After 2 weeks from the primary surgery, stitches were removed and TCZ-SC was re-injected. After 6 days, the patient developed surgical site infection and emergency debridement was required. Two patients (45-year-old female patient and 77-year-old female patient) reported inefficacy.

#### The drug retention rate of TCZ-SC

The retention rate was 92% (EO group) vs. 97% (Y group) at 24 weeks and 88% (EO group) vs. 90% (Y group) at 1 year after TCZ-SC administration, respectively. Log rank test demonstrated no significant difference between EO and Y group ( $P = 0.78$ ) (Fig. 5).

#### Discussion

In this study, we validated the effectiveness and safety of TCZ-SC on elderly-onset RA patients (aged above 65 years at RA onset and TCZ-SC administration). Upon TCZ-SC administration, the elderly onset RA (EO) group showed significant elevation in ESR (Table 1). However,

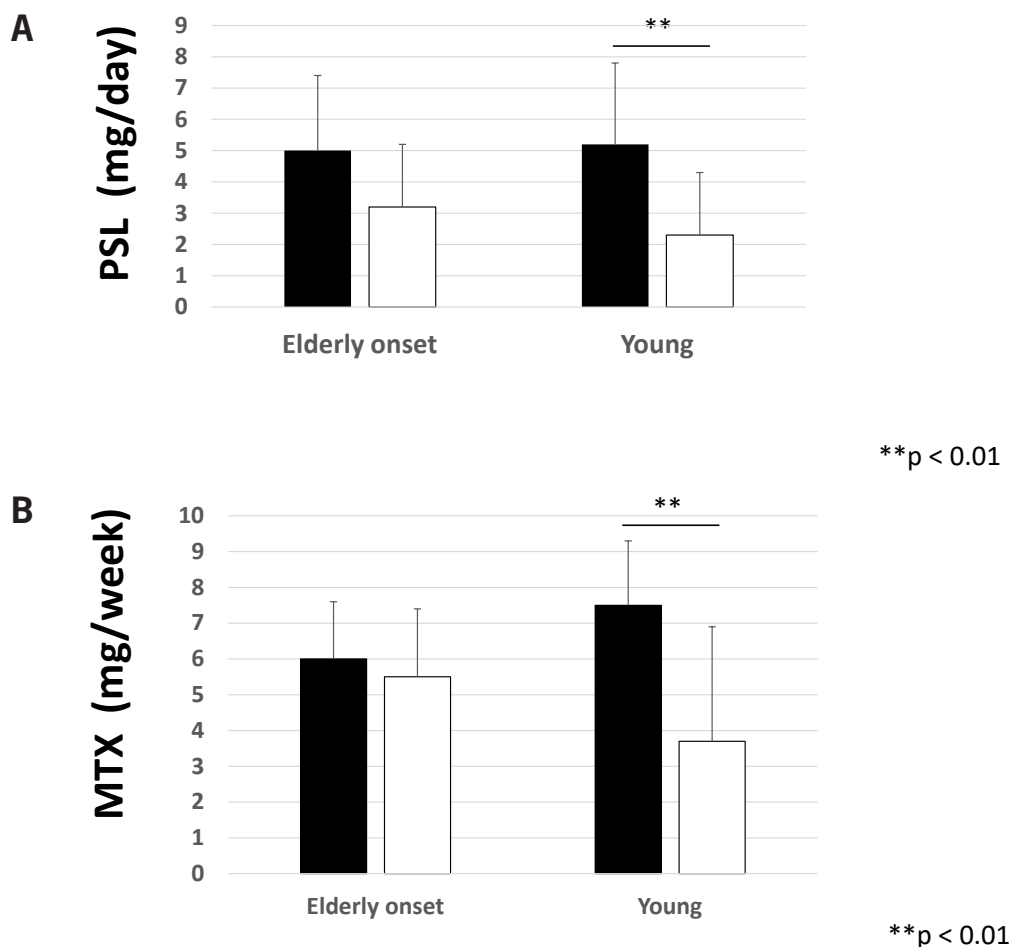


Fig. 4. Methylprednisolone dose and methotrexate dose.

(A) Methylprednisolone (PSL) dose.

In EO group (9 cases), the PSL daily dose was not significantly reduced from  $5.0 \pm 2.4$  mg/day upon subcutaneous tocilizumab (TCZ-SC) administration to  $3.2 \pm 2.0$  mg/day at 12 months after TCZ-SC administration ( $p = 0.064$ ). In Y group (9 cases), the PSL daily dose was significantly reduced from  $5.2 \pm 2.6$  mg/day to  $2.3 \pm 2.0$  mg/day ( $p = 0.0049$ ). At 12 months after TCZ-SC administration, the PSL daily dose in Y group was not significantly different from that in EO group ( $p = 0.33$ ).

Black bar: upon TCZ-SC administration. White bar: 12 months after TCZ-SC administration.

(B) Methotrexate (MTX) dose

In EO group (4 cases), the average MTX dose was not significantly reduced from  $6.0 \pm 1.6$  mg/week upon TCZ-SC administration to  $5.5 \pm 1.9$  mg/week at 12 months after TCZ-SC administration ( $p = 0.39$ ). In Y group (15 cases), the average MTX dose demonstrated significant reduction from  $7.5 \pm 1.8$  mg/week to  $3.7 \pm 3.2$  mg/week ( $p < 0.01$ ). However, no significant decrease was detected at the final follow up ( $p = 0.29$ ).

Black bar: upon TCZ-SC administration. White bar: 12 months after TCZ-SC administration.

both DAS28 and CDAI were significantly decreased at 3 months after TCZ-SC administration in both groups without significant differences between EO and Y groups (Figs. 1, 2). DAS28 remission rate and EULAR response rate was similar between the 2 groups. These findings indicate that TCZ-SC is comparably effective between EO and Y groups even in case with lower used rates of MTX. In addition, PSL daily dose could not be significantly reduced in EO group but reduced in Y group, suggesting that TCZ-SC can not only prominently induce remission state but also reduce PSL daily dose in Y group.

The self-injection rate of TCZ-SC in EO group was significantly lower than that in Y group (Table 1). The probable cause of this finding is that learning the self-injec-

tion technique is more difficult for EO group, and visiting our facility was easier for EO group because they are not employed.

TCZ is effective as a first- or subsequent-line medication in patients with moderate to severe RA (Dhillon 2014). The efficacy and safety of TCZ-SC are comparable with those of TCZ-IV (Nakashima et al. 2014). A recent report has also indicated that several randomized clinical trials showed non-inferiority of TCZ-SC to TCZ-IV (Mitchell and Jones 2016). In real-world clinical setting, the safety and effectiveness of TCZ-SC were evaluated in Japan. Overall, 784 (78.1%) RA patients were TCZ-naïve and 219 (21.8%) treated RA patients switched from TCZ-IV to TCZ-SC. Both groups showed improvement in CDAI and

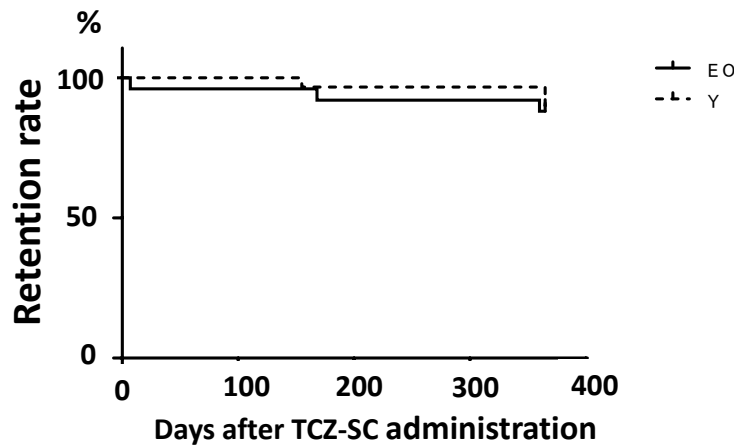


Fig. 5. The retention rate of TCZ-SC.

In EO group (25 cases), the retention rate was 92% at 24 weeks and 88% at 1 year after TCZ-SC administration. In Y group (30 cases), the retention rate was 97% at 24 weeks and 90% at 1 year after TCZ-SC administration. No significant difference was detected in the retention rate between the 2 groups by Log-Rank test ( $p = 0.78$ ).

DAS28 from baseline to week 26, and the authors concluded that TCZ-SC was effective in reducing disease activity and maintaining remission states (Atsumi et al. 2018).

Izumi et al. (2015) also demonstrated the clinical, functional, and structural outcomes of 115 RA patients initiating TCZ treatment and divided them into the TCZ+MTX group or without MTX (TCZ group). TCZ improved DAS28 to 2.1 from 5.0 at week 52, showing no significant difference between the groups. Clinical (DAS28 < 2.6), functional (Health Assessment Questionnaire (HAQ)-DI  $\leq 0.5$ ), and structural (total Sharp score ( $\Delta$ TSS)  $\leq 0.5$ ) remission rates in the TCZ and TCZ+MTX groups were 79.1%/63.8% ( $p = 0.10$ ), 62.8%/54.4% ( $p = 0.40$ ), and 70.0%/53.8% ( $p = 0.61$ ), respectively, and they concluded that TCZ was clinically, functionally, and radiographically effective and safe with or without low-dose MTX (Izumi et al. 2015).

A few reports reported the efficacy and safety of TCZ-SC in patients with EORA.

A retrospective study of TCZ use in 222 RA patients was conducted by dividing 2 aged groups, under 65 years and over 65 years (61 patients, 27.5%). After 6 months, over 65 years old group less often reached remission (27.8% vs. 45.6% under 65 years old,  $p = 0.02$ ) or good EULAR response (40.7% vs. 61.0% under 65 years old,  $p < 0.01$ ). Drug maintenance for TCZ and adverse events discontinuation rates were similar between the 2 age groups (Pers et al. 2015).

In another report, tocilizumab was introduced in 12 EORA patients aged > 70 years with existing treatments for RA (Morita et al. 2014). Of these, 10 cases were bio-naïve. The achievement rate of clinical remission (DAS28 < 2.3) was 80%. In addition, two cases achieved drug-free remission. The reported effects were mild pneumonia (one case) and herpes zoster virus infection (three cases).

Whether concurrent use of MTX with TCZ for elderly onset RA patients shows effectiveness remains unclear. For

elderly patients, a little report was acquired. For instance, Hidaka et al. (2018) demonstrated that comparable TCZ outcome for RA patients who were more than 70 years old (26 cases) compared with those who were less than 70 years old (41 cases). In the report, MTX dose was significantly lower in elderly patients (7.1 in more than 70 years old vs. 9.6 mg/week in less than 70 years old,  $p < 0.05$ ), suggesting that the significance of MTX in elderly patients are not so relevant. Our study also demonstrated that good effectiveness of TCZ-SC in EO group in spite of lower treated rates and doses of MTX.

In our study, the clinical remission rates reached to more than 75% in both groups and EULAR response showed that moderate response was dominant in elderly onset group similar to young group.

MMP-3 is a useful biomarker for detecting the effect of TCZ (Kaneko et al. 2012). In our study, serum MMP-3 levels were also decreased in both groups (Fig. 3). This decrease was somehow milder than in EO group than in Y group. Ishiguro et al. (2017) demonstrated that TCZ helped in the tapering of MTX and PSL doses in the real-world settings.

In our study, PSL daily dose was reduced (Fig. 4A), and significant decrease was acquired in PSL dose in Y group without flaring up the disease activity of RA, but not in EO group. In elderly-onset RA patients, PSL can be tapered well to prevent several adverse events due to steroid use, such as glucocorticoid-induced osteoporosis, steroid-induced cataract and glaucoma, and impaired glucose tolerance. In our study, significant PSL daily dose tapering was not determined in EO group upon 12 months although good clinical outcome was acquired by TCZ-SC.

The efficacy of MTX in elderly RA patients was reported comparable in young RA patients by comparing MTX and placebo with tumor necrosis factor therapy (Fleischmann 2003). Related to MTX, MTX treated doses in EO group and Y group was not so high. In addition,



MTX treated rates in EO group was significantly lower than that in Y group. We consider the reason as significant lower renal function (eGFR) in EO group.

The cessation rate due to adverse events was 4.6% in BREVACTA study (Kivitz et al. 2014) and 4.8% in SUMMACTA study (Burmester et al. 2014) and 1.7% in the MUSASHI study (Nakashima et al. 2014; Ogata et al. 2014).

All the three studies are the representative reports related clinical efficacy and safety about TCZ-SC for patients with RA with an inadequate response to DMARDs.

In our study, the cessation rate (6.8%) due to adverse events was higher than the rates reported in those studies. Only two cases (3.4%) of TCZ-SC cessation due to inefficacy in our study, suggesting that good retention rate of TCZ-SC was preserved in both groups.

Notably, this study has some limitations. First, the sample size was small to warrant generalized analysis results. Second, the HAQ and Sharp scores were not evaluated; hence, we cannot validate functional and structural remissions.

In conclusion, the clinical remission rate, EULAR response, and the retention rate in elderly onset RA patients were comparable to those in young patients by administering TCZ-SC up to 12 months. TCZ-SC showed good clinical outcome (effectiveness and safety) even in elderly-onset RA patients. Then TCZ-SC is a useful agent for patients with EORA.

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### Conflict of Interest

The authors declare no conflict of interest.

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