

Consideration of differences in drug usage between young-onset and elderly-onset rheumatoid arthritis with target of low disease activity.

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## Original article

### **Consideration of differences in drug usage between young-onset and elderly-onset rheumatoid arthritis with target of low disease activity**

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## **Abstract**

**Objectives:** Elderly-onset rheumatoid arthritis (EORA) is reported to differ from young-onset rheumatoid arthritis (YORA) with regard to patient background and drug treatment. We examined the amount of drug administered to patients who achieved low disease activity (LDA) for rheumatoid arthritis at our hospital.

**Methods:** Demographics, clinical history, and treatments were compared between patients with EORA (n=70) and YORA (n=190).

**Results:** There was a significant difference in the average age (73.8 vs. 57.8 years), disease duration (6.66 vs. 14.7 years), and sex (62.9% males vs. 83.7% females), but no difference in rheumatoid factor positivity (85.3% vs. 80.7%), anti-citrullinated peptide antibody positivity (86.5% vs. 87.7%), simplified disease activity index (4.28 vs. 4.59), and disease activity score 28-CRP (1.99 vs. 2.04) in the EORA and YORA groups, respectively. There were also no significant differences in prednisolone use (37.1% vs. 36.3%), amount of methotrexate administered (MTX) (1.45 vs. 1.41 mg), and MTX use (55.7% vs. 65.3%). However, the MTX dose (2.89 vs. 4.09 mg/week, p=0.011) and overall biologics use (32.9% vs. 56.3%, p=0.0012) were significantly lower in patients with EORA than in those with YORA.

**Conclusion:** Patients with EORA may be able to achieve LDA with lower drug dosage than those with YORA.

## ***Introduction***

With the development of new therapies, such as biological disease-modifying anti-rheumatic drugs for rheumatoid arthritis (RA), an increasing number of elderly patients with RA are seeking treatment in the current ageing population. Furthermore, the onset age of RA has been trending higher [1]. Elderly-onset RA (EORA) is defined as RA that develops after 60 years of age and is shown to differ from young-onset rheumatoid arthritis (YORA) with regard to patient demographics, clinical history, and drug treatment [2]. Age at disease onset is known to be an indicator of disease activity, disease severity, and comorbidities [3-10]. Some studies suggest that prognosis of EORA may be poor because some patients with EORA have dysfunctions and comorbidities that limit appropriate treatment; prognosis of YORA is also poor because patients with YORA require more treatment. Furthermore, it is unclear whether the possible difference in prognosis between patients with YORA and EORA is directly due to age at onset or indirectly due to differences in treatment. Although many EORA cases have an acute onset, cases with polymyalgia rheumatica (PMR)-like symptoms that are negative for rheumatoid factor (RF) have recently been observed at a relatively higher rate [11]. In fact, it is occasionally difficult to distinguish between EORA and PMR in clinical settings. For patients with either EORA or YORA, the approach of ‘treat-to-target’ is necessary [12, 13], although it is considered that EORA should be treated with the goal of reaching low disease activity (LDA) from the viewpoint of side effects of the administered therapeutic drugs [12]. Regarding drug efficacy, some patients with EORA have comorbidities or health-related problems and are typically excluded from randomised controlled trials. Therefore, the efficacy of disease-modifying antirheumatic drugs, including tumour necrosis factor inhibitors or methotrexate (MTX), demonstrated by randomised controlled trials is different from that observed in clinical practice because of the variation in age, treatment protocols, inclusion of patients treated outside the targeted therapeutic strategy, less stringent treatment goals (LDA), and more co-morbidities found in various trials [5]. Therefore, an actual cohort study is needed to evaluate EORA characteristics. Thus, in this study, we examined the number of RA drugs administered to patients with EORA or YORA who achieved LDA at our **medical facility**.

## ***Patients and Methods***

Patients with RA attending the outpatient clinic of the Department of Orthopedic Surgery, Shiga University of Medical Science Hospital, Japan, from October to December 2018 were invited to participate in this study. Patients were at least 18 years of age and fulfilled the 1987 American College of Rheumatology (ACR) revised criteria for RA [14, 15]. EORA was defined as disease onset at 60 years of age or more. Informed consent was

obtained, and the study was carried out according to the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. This study was approved by the Shiga University of Medical Science Hospital Ethical Committee (R2017-093). We surveyed a total of 339 patients: 94 with EORA and 245 with YORA. Patients were treated according to RA treatment guidelines of the Japan College of Rheumatology [16]. MTX 6 mg/week was administered to patients without complications, and MTX 2–4 mg/week was administered to patients with risk factors for side effects, such as lung disease (history of interstitial pneumonia, pulmonary fibrosis, tuberculosis, etc.) and decreased renal function ( $eGFR \leq 60$  mL/min/1.73m<sup>2</sup>). Patients were given additional conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) other than prednisolone (PSL) and MTX, depending on disease activity after the start of treatment. LDA was defined as a simplified disease activity index (SDAI) [17]  $\leq 11$ . The number of patients who achieved LDA was 260 in the EORA group (achievement rate 74.5%) and 190 in the YORA group (achievement rate 77.2%), and we investigated their demographics, clinical background, and treatment protocols. SDAI and disease activity score 28 with C-reactive protein (DAS28-CRP) [18] were used to assess the disease activity of the patients. PSL, MTX, csDMARDs, and various biologics were evaluated as the target drugs.

### Statistical analysis

Data are expressed as the mean  $\pm$  SD for baseline measurements. The data were analysed using IGOR Pro 8 (WaveMetrics, Inc. 10200 SW Nimbus, G-7 Portland, OR 97223). Statistical comparisons were evaluated using the Student's *t*-test, and differences were considered significant at  $p < 0.05$ .

### Results

With respect to the patients' demographics and clinical background, there were significant differences between the EORA and YORA groups for mean age, mean disease duration, and female sex, whereas the difference was not significant with regard to antibody positive rate, SDAI, or DAS28-CRP. The average age was  $73.8 \pm 6.30$  and  $57.8 \pm 12.5$  years, disease duration was  $6.67 \pm 4.76$  (1–22) and  $14.7 \pm 11.2$  (1–55) years, and the proportion of females was 62.9% and 83.7%, in the EORA and YORA groups, respectively. Furthermore, RF positivity was 85.3% and 80.7%, anti-citrullinated peptide antibody positivity was 86.5% and 87.7%, SDAI was 4.28 and 4.59, and DAS28-CRP was  $1.99 \pm 0.67$  and  $2.04 \pm 0.66$ , in the EORA and YORA groups, respectively (Table 1). The eGFR, which is an indicator of renal function, was  $62.9 \pm 21.9$  mL/min/1.73m<sup>2</sup> in the EORA group and  $74.1 \pm 22.0$  mL/min/1.73m<sup>2</sup> in the YORA group. The serum albumin level, which is an index of nutritional status, was  $3.28 \pm 0.48$  g/dL in the EORA group and  $4.44 \pm 0.42$  g/dL in the YORA group. As for the treatments administered to the patients, the rates of PSL use (37.1% vs. 36.3%), PSL dosage (at the start of therapy,

1.52±2.28 (1–11) vs. 2.22±3.56 (2.5–15) mg/day; current treatment, 1.45±2.40 (1–5) vs. 1.41±2.88 (1–10) mg/day), the rates of csDMARDs use (60.0% vs. 51.6%), and MTX usage rate (55.7% vs. 65.3%) were not significantly different between the groups. On the other hand, MTX weekly administration (at the start of therapy, 3.20±2.92 (2–10) vs. 5.07±3.13 (2–12) mg/week; current treatment, 2.89±2.98 (2–10) vs. 4.09±3.48 (2–10) mg/week,  $p<0.01$ ) and biologics usage rate (32.9% vs. 56.3%,  $p<0.01$ ) were significantly lower in the EORA group than in the YORA group (Table 2a and b). However, when comparing the biologics group and the non-biologics group, the MTX dose in the biologics group was significantly lower in the EORA group than in the YORA group at the start of treatment (3.92±3.03 vs. 5.37±2.94 mg/week,  $p<0.01$ ). However, no significant difference was observed with the current treatment (2.92±2.82 vs. 3.23±2.71 mg/week). On the other hand, in the non-biologics group, LDA could be reached in the EORA group at a significantly smaller dose of MTX than in the YORA group at both the start of treatment and the current treatment (Table 2b). Regarding comorbidities in our study groups, there was a significant difference between the EORA and YORA groups in terms of hypertension and diabetes, and a tendency of increased incidence of interstitial pneumonia was seen in the EORA group ( $p=0.06$ ) (Table 3). Furthermore, the incidence of MTX disorders was 12.5% in the EORA group and 12.7% in the YORA group, which was not statistically significant. This result suggests that the amount of MTX used could be reduced in the EORA group due to the influence on comorbidity rather than the control of disease activity. The individual biologics used in each group are listed in Table 4. Tumour necrosis factor inhibitors represented the majority of biologics in each group, although specific agents differed significantly. Etanercept was the most commonly used first biologic drug for both, EORA and YORA (48.1% and 44.2%, respectively). The distribution of the first biologics used was almost the same between patients with YORA and those with EORA (Table 4, at the start of therapy). Drug survival of the first biologic after 1 year was 51.2% for patients with EORA compared with 52.7% for patients with YORA. First biologics failure was observed in 6 cases in the EORA group and 28 cases in the YORA group, and second biologics failure was observed in 4 cases each in both groups. Finally, in current treatment, tocilizumab in YORA group (27.6%), certolizumab pegol (8.69%), and abatacept in EORA (21.3%) group were more frequently used among patients of their respective groups ( $p<0.01$ ). Table 5 shows the usage rate of csDMARDs. Only iguratimod showed a significantly higher usage rate in the YORA group, but no significant difference was observed for other drugs.

### **Discussion**

RA is the most prevalent inflammatory synovitis affecting 2–2.3% of the geriatric population [19]. The differential diagnostic possibilities for EORA are PMR, pseudogout, reflex sympathetic dystrophy, and

osteoarthritis; these must be excluded before a definite diagnosis of EORA is made [20]. Since a precise diagnosis of EORA is difficult, it takes a long time to confirm the diagnosis of the disease. Our study found that YORA had a significantly longer treatment period than EORA. This may be because our medical facility is a referral centre for many cases from the local hospitals or clinics, or there are many cases where diagnosis is difficult and it takes time to decide the treatment policy. A striking female dominance characterises many autoimmune diseases and oestrogen-activated humoral immunity. Sex steroids contribute to the development of autoimmune diseases. It is well known that women are about three times more likely to be affected than men, but studies of the elderly group show reduced sex differences [21, 22]. In our study, the female ratio in EORA decreased by about 20%. **This result suggests that our study group is not significantly different from other research groups.** A significant percentage of patients with EORA have symptoms such as bilateral pain and PMR symptoms such as neck and torso stiffness, shoulders and arms stiffness, and prolonged morning stiffness in the hips and thighs at various times during the follow-up. Peripheral arthritis in both hands can make the confirmative diagnosis of PMR and EORA difficult. Both illnesses have clinical presentations varying from classic RA to PMR symptoms. Therefore, the diagnosis of PMR or RA should be made at different times in the same patient, depending on the clinical manifestation of the disease [23, 24]. **In this study, the possibility of patients with PMR being included was limited as much as possible based on the initial diagnosis at study enrolment and its confirmation at the end of the study period.** In addition, in other studies, patients were considered to have PMRs with a broader clinical spectrum of the disease appearing at the end of the observation period. Patients with EORA have been reported to have an acute onset with both small and large joint lesions and more frequent PMR-like symptoms [25]. Since our report is limited to cases that have acquired low disease activity, PMR-like symptoms have not been fully analysed. Future research should examine the details of each case.

Inflammatory findings such as increased erythrocyte sedimentation rate and C-reactive proteins are stronger in EORA, and anaemia associated with chronic inflammation is more common in EORA than in YORA [22, 26, 27]. The frequency of a positive RF is more in EORA than in YORA. It is often reported that the rate of a positive RF is low in YORA [27, 28]. On the other hand, 12% of healthy people over the age of 60 years are reported to be RF positive [29]. It is said that the anti-CCP antibody positivity rate in patients with YORA is 92.7%, and that patients with EORA have a lower anti-CCP antibody positive rate than those with YORA [30]. However, we did not find any significant differences in both RF and anti-citrullinated peptide antibody between the two groups (Table 1), indicating that it does not influence the diagnosis of patients with LDA. However, it is

necessary to fully understand the characteristics of the elderly and consider existing policies when determining their treatment.

In general, elderly patients are characterised by decreased renal function and decreased serum albumin levels [31-33]. In our survey, the eGFR and the serum albumin level in the EORA and YORA groups, respectively, which are consistent with previous reports. Comparing the comorbidities in our study group, there was a significant difference between the EORA and YORA groups in terms of hypertension and diabetes, and a tendency to increase in interstitial pneumonia. No significant differences were observed with regard to malignant tumours, renal insufficiency requiring dialysis, hepatitis B virus infection, or vascular diseases, such as cerebral infarction, in both groups (Table 3). This does not mean that there were no differences between patients with EORA or YORA and other general patients with regard to comorbidities. Since our medical facility is a regional base hospital, it is possible that there were more patients with complications than general patients. As a result, the MTX dose administered may have been reduced according to the protocol. Interestingly, there was a significant difference in the amount of MTX at the time of introduction of biologics between the EORA ( $3.92 \pm 3.03$  mg/week) and the YORA ( $5.37 \pm 2.94$  mg/week) groups, but there was no significant difference in the amount of MTX in the current treatment term ( $2.92 \pm 2.82$  vs.  $3.23 \pm 2.71$  mg/week). This finding indicates that drug introduction may reduce the dose of MTX in cases where biologics can be used to achieve LDA, regardless of RA onset time or current age. At the time of introduction of biologics, there was no difference in the ratio of drugs used between EORA and YORA. However, due to various factors, such as the effects or side effects of the drug and the usability of MTX, there was a difference in the ratio of drugs used in the current treatment term. Additionally, this observation could potentially explain the significant differences observed in patients with YORA receiving abatacept, which is said to have few side effects, compared to EORA patients. Moreover, tocilizumab may have been administered to many patients with YORA because MTX could not be administered (Table 4). Therefore, it is necessary to collaborate with other local hospitals and clinics in the future to investigate a larger patient group. For csDMARDs, there was no difference in the usage ratio of each drug between the EORA and YORA groups except for iguratimod (Table 5). It is as yet unclear why iguratimod has a higher usage rate in the YORA group than in the EORA group. However, since this drug was launched in 2012 and is the newest drug available, it is often administered in concomitance with other drugs. Our results suggest that LDA was achieved in the EORA with a smaller drug dose than in the YORA group. However, in general, elderly patients often experience higher rates of side effects, which are likely to become serious leading to a longer recovery time. Therefore, medical staff such as doctors and pharmacists need to

carefully administer medications and reduce the amount of the drug required for the desired results. There have been several reports on RA and LDA [34], but few have described medication content [35]. Furthermore, no previous studies report on the drugs used for patients with EORA and YORA, as we do in this study, which we believe to be highly useful. As a limitation, this study only extracted cases for which LDA had already been obtained for both groups, so there is a possibility that the results may differ from the actual treatment patient group. In addition, since our medical facility is a regional base hospital, it is possible that the patient group at the time of intervention had a higher proportion of difficult-to-treat cases, including patients with comorbidities, than the general patient group.

### ***Conclusion***

The age of onset of RA has been increasing with an increase in the life expectancy of the society. Therefore, it is important to consider the features of EORA and YORA when considering the approach to therapy. In the present investigation, we considered achievement of LDA rather than remission as the goal of treatment, and our findings indicate that patients with EORA may be better able to achieve that goal with a lower MTX dosage and biological product usage than those with YORA.

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### ***Conflict of interest***

None.

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## Tables

Table 1. Demographic characteristics of patients with elderly-onset rheumatoid arthritis (EORA) and young-onset rheumatoid arthritis (YORA).

	EORA	YORA
LDA achievement rate (%)	74.5	77.6
Average age (yrs)	73.8±6.30**	57.8±12.5
Average onset age of RA (yrs)	67.1±6.25	43.1±10.8
Average disease duration (yrs)	6.67±4.76	14.7±11.2**
Female rate (%)	62.9	83.7**
RF positive rate (%)	85.3	80.7
ACPA positive rate (%)	86.5	87.7
SDAI	4.28±3.19	4.59±2.99
DAS28CRP	1.99±0.67	2.04±0.66

Values are given as mean±SD. \*\* $p < 0.01$  was considered to be statistically significant.

Abbreviations: RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibody; SDAI, simplified disease activity index; DAS28CRP, disease activity score (DAS) 28-CRP

Table 2. Medication use in patients with elderly-onset rheumatoid arthritis (EORA) and young-onset rheumatoid arthritis (YORA).

Table 2a.

	EORA	YORA
Rate of PSL use(%)	37.1	36.3
Rate of csDMARDs use (%)	60.0	51.6
Rate of MTX use (%)	55.7	65.3
Rate of Biologics use (%)	32.9**	56.3

Table 2b.

	EORA		YORA	
	At the start of therapy	Current treatment	At the start of therapy	Current treatment
PSL dosage (mg)	1.52±2.28	1.45±2.40	2.22±3.56	1.41±2.88
MTX dosage (mg/w)	3.20±2.92**	2.89±2.98**	5.07±3.13	4.09±3.48
MTX with Biologics	3.92±3.03**	2.92±2.82	5.37±2.94	3.23±2.71
MTX without Biologics	2.83±2.85**	2.04±2.78**	4.63±3.34	5.27±3.09

Values are given as mean±SD. \*\* $p < 0.01$  was considered to be statistically significant.

Abbreviations: PSL, prednisolone; MTX, methotrexate.

Table 3. Rheumatoid arthritis-related comorbidities in patients with elderly-onset rheumatoid arthritis (EORA) and young-onset rheumatoid arthritis (YORA).

Comorbidities, n (%)	EORA	YORA
Interstitial pneumonia	14 (20.0)	21 (11.1)
Hypertension	15 (21.4)**	18 (9.47)
Diabetes	6 (8.57)**	1 (0.53)
Malignant tumor	6 (8.57)	12 (6.32)
Renal insufficiency (with dialysis)	3 (4.29)	6 (3.16)
Stroke	2 (2.86)	3 (1.58)
Hepatitis B	3 (4.29)	5 (2.63)

\*\* $P < 0.01$  was considered to be statistically significant.

Table 4. Biologics used in patients with elderly-onset rheumatoid arthritis (EORA) and young-onset rheumatoid arthritis (YORA).

Drug name of Biologic, n (%)	EORA		YORA	
	At the start of therapy	Current treatment	At the start of therapy	Current treatment
Infliximab	3 (11.1)	4 (17.4)	15 (13.3)	16 (15.2)
Etanercept	13 (48.1)	8 (34.8)	50 (44.2)	38 (36.2)
Adalimumab	2 (7.40)	1 (4.35)	9 (7.96)	6 (5.71)
Golimumab	2 (7.40)	1 (4.35)	6 (5.30)	5 (4.76)
Certolizumab pegol	0 (0)	2 (8.69)**	4 (3.53)	2 (1.91)
Tocilizumab	4 (14.8)	2 (8.69)	18 (15.9)	29 (27.6)**
Abatacept	3 (11.1)	5 (21.3)**	11 (9.73)	9 (8.57)
Total	27 (100)	23 (100)	113 (100)	105 (100)

\*\* $p < 0.01$  was considered to be statistically significant.

Table 5. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) used in patients with elderly-onset rheumatoid arthritis (EORA) and young-onset rheumatoid arthritis (YORA).

Drug name of csDMARDs, n (%)	EORA	YORA
Salazosulfapyridine	26 (57.8)	59 (49.1)
Bucillamine	2 (4.44)	6 (5)
Iguratumod	2 (4.44)	17 (14.2)**
Tacrolimus	15 (33.3)	36 (30.0)
Leflunomide	0 (0)	2 (1.67)
Total	45 (100)	120 (100)

\*\* $p < 0.01$  was considered to be statistically significant.