Rheumatology Advances in Practice, 2024, **8(1)**, rkae019
https://doi.org/10.1093/rap/rkae019
Advance access publication 9 February 2024
Original Article

British Society for Rheumatology
RHEUMATOLOGY ADVANCES IN PRACTICE
OXFORD

Clinical science

Effectiveness and safety of treat-to-target strategy for methotrexate-naïve rheumatoid arthritis patients >75 years of age

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Abstract

Objectives: To identify differences in effectiveness and safety of a treat-to-target (T2T) strategy comparing late-onset MTX-naïve RA patients (LORA) ≥75 or <75 years of age.

Methods: Treatment was adjusted to target low disease activity with conventional synthetic DMARDs followed by biologic DMARDs (bDMARDs) in LORA ≥75 years ($n = 98$, mean age 80.0 years) and LORA <75 years ($n = 99$) with moderate–high disease activity. Achievement of Simplified Disease Activity Index (SDAI) remission at week 156 by non-responder imputation analysis was evaluated as a primary outcome.

Results: LORA ≥75 years had more comorbidities than LORA <75 years, but SDAI and ACPA positivity were similar at baseline. Of the LORA ≥75 years, 70.4% started MTX and 34.1% and 37.1% received a bDMARD at week 52 and 156, respectively (very similar to the LORA <75 years). Glucocorticoid use was more frequent in the LORA ≥75 years than in the LORA <75 years. Comorbidities/adverse events more frequently contributed to the reasons for non-adherence to T2T in the LORA ≥75 than in the LORA <75. At week 156, 32.7% of the LORA ≥75 and 66.7% of the LORA <75 achieved SDAI remission ($P < 0.001$). The cumulative incidence of serious adverse events (SAEs) over 156 weeks was 42.8% in the LORA ≥75 and 22.1% in the LORA <75. Multivariable analysis indicated an increased risk of SDAI non-remission at week 156 in the LORA ≥75 [odds ratio 2.82 (95% CI 1.29. 6.14)] after adjusting for comorbidities at baseline, non-adherence to T2T and SAEs.

Conclusions: It was more difficult to achieve remission in the LORA ≥75 patients than in the LORA <75 patients due to both poor treatment response and safety issues.

Lay Summary

What does this mean for patients?

The proportion of patients ≥75 years of age with rheumatoid arthritis (RA) is increasing. However, it is not known whether a standard treatment strategy with the goal of low disease activity (i.e. where your symptoms are under control) would be beneficial in people with late-onset RA. Late-onset RA is where people develop RA at >60 years of age. Our study investigated the effectiveness and safety of treatment in people ≥75 years of age with late-onset RA. We found that this age group had more comorbidities (i.e. where a person has more than one disease at the same time) than people ages 60–74 years. Comorbidities and other medical problems prevented optimal treatment in the ≥75 group more so than in the 60- to 74-year group. Despite similar disease activity when starting treatment, only 32.7% of the ≥75 group were in remission (i.e. had very few or no RA symptoms) after 3 years of treatment, compared with 66.7% of the 60- to 74-year age group. Serious medical problems were more common in the ≥75 group. Our findings suggest that a poorer response to treatment and a higher rate of serious medical problems make it more challenging for people ≥75 years of age to reach remission. We need to consider and address optimal treatment strategies for this group of people in the near future.

Keywords: late-onset rheumatoid arthritis, age ≥75 years, treat-to-target, SDAI remission, comorbidities, serious adverse events.

Key messages

- Achieving remission using a T2T strategy was more difficult in LORA ≥75 patients than in LORA <75 patients.
- LORA ≥75 patients had significantly more SAEs and non-implementation of T2T than LORA <75 patients.
- SAEs and non-implementation of T2T also contributed to non-achievement of remission in LORA ≥75 patients.

Received: 9 October 2023. **Accepted:** 24 January 2024

Introduction

The proportion of elderly patients with RA is increasing. Older RA patients are more likely to experience difficulties in the activities of daily life than older people without RA [1]. According to the Japanese National Database, 60.8% of 825 000 patients with RA were ≥65 years of age, the largest age group being 70–79 years old (28.6%), followed by 60–69 years (26.4%) [2]. A recent meta-analysis of observational studies, mostly of patients with a longer disease duration, concluded that older patients have a slightly worse response to treatment than younger patients [3]. Whereas subanalysis of randomized controlled trials (RCTs) for patients with shorter disease duration documented no differences in treatment outcomes between older and younger participants [4–7]. In younger patients it has been established that a treatment strategy based on treat-to-target (T2T) retards the progression of joint destruction and improves physical function [8–10].

In order to clarify the effectiveness and safety of T2T in late-onset RA (LORA), we developed the CRANE cohort (Choju registry of RA treated with non-biologic DMARDs and biologics in elderly patients in Japan) [11, 12]. About 60% of patients with LORA who adhered to the T2T of low disease activity (LDA) for 3 years achieved remission after 3 years, with acceptable safety [12].

An epidemiological study of a non-RA population suggested that physical function of elderly patients has improved recently and 75 years is an optimal cut-off age for the older population [13]. However, it was not obvious whether the implementation of T2T would improve disease activity and physical function in the older population ≥75 years of age. Therefore we investigated the effectiveness and safety of T2T of LDA in MTX-naïve older LORA patients ≥75 years of age (LORA ≥75) relative to patients 60–74 years of age (LORA <75) as a control.

Methods

Study design and patients

CRANE was a prospective monocentric cohort study at the Tokyo Metropolitan Geriatric Hospital enrolling patients between 2008 and 2015. Eligible participants were MTX-naïve patients with disease onset at age ≥60 years, with active RA [28-joint DAS with ESR (DAS28-ESR) ≥3.2], according to the 1987 revised ACR classification criteria. This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research in Japan. The Ethics Committee of Tokyo Metropolitan Geriatric Hospital approved the protocol of this study (240117467) and all patients provided written informed consent.

Procedures

Treatment was adjusted to target LDA [i.e. Simplified Disease Activity Index (SDAI) <11.0 or DAS28-ESR <3.2] based on shared decisions of the patient and the attending rheumatologist. Treatment was initiated with conventional synthetic DMARDs (csDMARDs), followed by biologic DMARDs (bDMARDs) [11]. If a patient had active interstitial lung disease, chronic hepatitis C or renal dysfunction with an estimated creatinine clearance (CrCl) <30 ml/min, csDMARDs other than MTX were considered. Treatment with MTX and folic acid at 5 mg/week was initiated in patients with poor prognostic factors (i.e. high disease activity, ACPA positive, functional limitation or bone erosions by radiography) and MTX was increased to the maximum tolerable dose. Treatment was intensified in patients who did not achieve LDA at week 24 using a TNF inhibitor (TNFi) with or without MTX based on the 2008 ACR recommendations and the 2008 Japan College of Rheumatology guidelines [14, 15]. As a second bDMARD, a different TNFi with or without MTX, or tocilizumab or abatacept was used. Glucocorticoid (GC) tapering was at the discretion of an attending rheumatologist. The definition of non-implementation of the T2T strategy was described in a previous study [12] as follows: lack of a EULAR response and no intensification of the treatment regimen at week 12 and not achieving LDA and no intensification of treatment at weeks 24, 36, 52, 76, 104 or 128. The reasons for non-implementation were dichotomized as either the patient's decision or the presence of comorbidities/adverse events (AEs). Non-implementation of T2T was not deemed as a discontinuation of observation. Patients who received an increased dose of GCs for worsening RA-associated extra-articular diseases or other rheumatic disease manifestations were censored at the time of the GC dose increase. Discontinuation of observation was defined as the earliest of lost to follow-up from the outpatient clinic, increased dose of GCs due to the comorbidities, withdrawal of consent or death.

We divided the patients in our cohort into LORA ≥75 and LORA <75 and performed the following analyses.

Primary outcome

SDAI remission (SDAI ≤3.2) at week 156 was the primary outcome. Non-responder imputation (NRI) approaches were applied for estimating the proportion of patients achieving SDAI remission.

Secondary outcomes

SDAI remission, LDA (SDAI <11), normal physical function [Health Assessment Questionnaire–Disability Index (HAQ-DI) ≤0.5], clinically relevant radiological progression [CRRP; changes in the van der Heijde–modified total Sharp score (ΔmTSS)/year >smallest detectable change of 2.1] at week 52 and SDAI LDA (HAQ-DI ≤0.5) at week 156 were assessed. NRI approaches were applied for achievement of these binary outcomes. Serious adverse events (SAEs) of special interest [infections requiring hospitalization, deterioration of RA-associated lung disease, other autoimmune disease, bone fractures, cardiovascular disease (CVD), malignancy] during the observation period were also evaluated [11].

Statistical analysis

Student's *t*-test and the Mann–Whitney test were used to compare continuous variables depending on their distribution, and the chi-squared test and Fisher's exact test were used for categorical variables. Cumulative rates and median time to the first events for patients stratified by age were analysed using the Kaplan–Meier method and the logrank test. To evaluate the association between LORA ≥75 and non-achievement of SDAI remission, we performed a multivariate logistic regression analysis adjusting for baseline factors (model 1). Non-implementation of T2T and the occurrence of SAEs over 3 years were expected to impact non-SDAI remission, and these two factors were added to model 1 as covariates and analysed (model 2). Analytical procedures

were performed using SPSS version 26 (IBM, Armonk, NY, USA). All reported *P*-values were two-tailed and the level of significance was set at $P < 0.05$.

Results

Baseline characteristics of LORA ≥75 and LORA <75

The mean age of the LORA ≥75 ($n = 98$) and LORA <75 ($n = 99$) patients was 80 years (S.D. 3.9) and 68.9 years (S.D. 3.8), respectively, and the duration of disease and ACPA and RF positivity were similar between the two groups. The baseline CRP level was significantly higher in the LORA ≥75 patients than in the LORA <75, and the SDAI was numerically higher in the former. Baseline mTSS and HAQ-DI were significantly higher in the LORA ≥75 than in the LORA <75 patients (Table 1). In the LORA ≥75 group, the proportion of patients with each comorbidity at baseline was 63.3% for chronic kidney disease (CrCl <60 ml/min), 65.3% for hypertension, 35.7% for osteoporosis and 13.3% for a history of hospitalized infection; these values were all significantly higher in the LORA ≥75 than in the LORA <75 patients. The proportion of chronic lung disease was 25.5% in the LORA ≥75 patients, but this was not significantly different from the LORA <75 (Table 1).

Treatment of the LORA ≥75 and LORA <75 patients

MTX and csDMARDs other than MTX were initiated in 76 (77.6%) and 22 (22.4%) of the 98 LORA ≥75 patients and in 84 (84.8%) and 15 (15.2%) of the 99 LORA <75 patients, respectively. In the patients initiating treatment with MTX ± other csDMARDs and not achieving LDA by week 24, a bDMARD was started in 32 (42.1%) with MTX and 3 (3.9%) without MTX of the 76 LORA ≥75 patients, and in 27 (32.1%) with MTX and 2 (2.3%) without MTX of the 84 LORA <75 patients. In patients initiating treatment with csDMARDs other than MTX and not achieving LDA by week 24, a bDMARD was administered in 1 (4.5%) with MTX and 8 (36.4%) without MTX of the 22 LORA ≥75 patients and in 1 (6.7%) with MTX and 6 (40.0%) without MTX of the 15 LORA <75 patients. Subsequent changes to a bDMARD with a different mechanism of action were reported in 3 of the LORA ≥75 and 6 of the LORA <75 patients. None of the LORA ≥75 and two of the LORA <75 patients received a third bDMARD with a different mechanism of action (Fig. 1). Although we did observe cases of switching from a TNFi to another TNFi due to secondary failure, these were not counted as second or third bDMARDs. The frequency of switching from a TNFi to another TNFi, IL-6 inhibitor and abatacept during a 3-year period was similar between the LORA ≥75 and LORA <75 patients (Table 2).

The proportion of MTX use during the 3-year observation period was almost the same in the LORA ≥75 and LORA <75 patients, while MTX doses and cumulative doses of MTX over 3 years were lower in the former (Table 2). The time to discontinue MTX was significantly shorter in the LORA ≥75 patients, who started MTX at week 0, than in the LORA <75 patients (Supplementary Fig. S1A, available at *Rheumatology Advances in Practice* online). The time to start the first bDMARD was not significantly different between the two groups (Supplementary Fig. S1B, available at *Rheumatology Advances in Practice* online), but the proportions of patients using bDMARDs tended to be higher in the

Table 1. Baseline characteristics of LORA <75 and LORA ≥75 patients

Characteristics	LORA <75 ($n = 99$)	LORA ≥75 ($n = 98$)	*P*-value
Age, years, mean (S.D.)	68.9 (3.8)	80.0 (3.9)	<0.001*
Female, %	72.7	70.4	0.718
Body weight, kg, mean (S.D.)	54.7 (10.0)	50.7 (10.0)	0.005*
Symptom duration, years, median (IQR)	0.5 (0.3–1.0)	0.5 (0.3–2.1)	0.465
DAS28-ESR, mean (S.D.)	5.96 (1.28)	6.24 (1.07)	0.098
SDAI, mean (S.D.)	33.9 (16.5)	38.4 (16.0)	0.052
CRP, mg/dl, median (IQR)	1.32 (0.41–3.73)	2.68 (0.78–5.51)	0.018*
mTSS, median (IQR)	4.0 (1.0–10.3)	7.0 (1.8–14.3]	0.036*
Erosion score, median (IQR)	1.5 (0.0–4.1)	2.0 (1.0–6.0)	0.132
JSN score, median (IQR)	2.0 (0.0–6.1)	4.0 (0.0–8.5)	0.080
HAQ-DI, median (IQR)	0.81 (0.34–1.50)	1.25 (0.63–1.88)	0.003*
Positive anti-CCP antibody, %	68.7	67.3	0.840
Positive RF, %	64.6	56.1	0.221
Smoking history, %	50.5	28.1	0.001*
Chronic lung diseases, %	22.2	25.5	0.588
Interstitial lung disease, %	13.1	18.4	0.313
CrCl <60 ml/min, %	21.2	63.3	0.001*
CrCl <30 ml/min, %	1.0	6.1	0.118
Cardiovascular disease, %	11.1	19.4	0.106
Diabetes mellitus, %	21.2	19.4	0.750
Hypertension, %	45.5	65.3	0.005*
Hyperlipidaemia, %	25.3	24.5	0.901
Cerebrovascular disease, %	3.0	7.1	0.161
Osteoporosis, %	19.2	35.7	0.009*
Osteoarthritis, %	10.1	12.2	0.633
Past history of malignancy, %	8.1	13.3	0.238
Past hospitalized infection, %	4.0	13.3	0.021*

* Statistically significant at $P < 0.05$.
IQR: interquartile range; JSN: joint space narrowing.

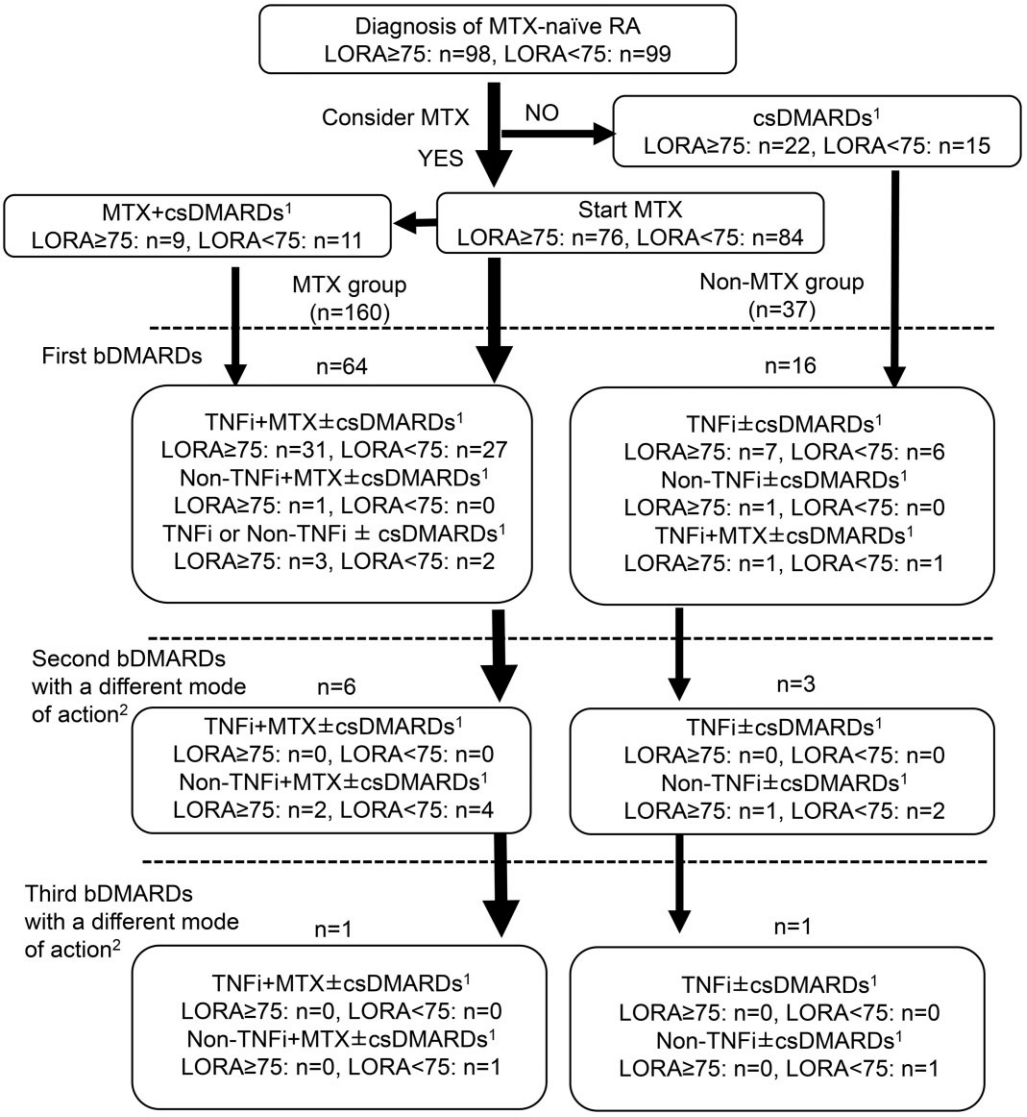

Figure 1. Treatment flowchart for LORA ≥75 and LORA <75. MTX was started in 160 patients (LORA ≥75: $n=76$; LORA <75: $n=84$). One LORA ≥75 patient received MTX and TNFi at baseline and was counted in the MTX group. Other csDMARDs were started in 37 patients (LORA ≥75: $n=22$; LORA <75: $n=15$). Five cases of other csDMARD failures received bDMARDs at baseline and were counted in the non-MTX group. In the MTX and non-MTX groups, a first bDMARD was started in 64 and 16 patients, a second bDMARD with a different mode of action in 6 and 3 patients and a third bDMARD, again with a different mode of action, in 1 and 1 patient, respectively. [1]csDMARDs other than MTX. [2]Although we did observe cases of switching from TNFi to another TNFi due to secondary loss of response, these were not counted as second or third bDMARDs

LORA ≥75 patients at all time points (Table 2). The number of bDMARDs used over 3 years was similar in the LORA ≥75 and LORA <75 patients. The proportion of GC use and cumulative doses of GC over the 3-year period were significantly higher in the LORA ≥75 than the LORA <75 patients (Table 2).

Adherence to the T2T strategy in the LORA ≥75 and LORA <75 patients

The proportion of T2T non-adherence was 41.8% ($n=41$) in the 98 LORA ≥75 patients, which was significantly higher than in the 99 LORA <75 patients [$n=28$ (28.3%)] (Table 2). However, 18 and 11 of these 41 LORA ≥75 patients showed non-adherence at only one and two time points over the 3 years of the study, respectively. The patient's decision accounted for similar proportions as the reason for non-adherence to T2T in the two groups, but non-adherence due to comorbidities/AEs was significantly more common in the LORA ≥75 than in LORA <75 patients (Table 2). Twenty-nine (29.6 %) of the LORA ≥75 patients and eight (8.1%) of the LORA <75 patients discontinued the observation (Table 2). Of the 29 LORA ≥75 patients, observation was discontinued in 10 due to an increased dose of GCs for RA-ILD or IgA vasculitis, 10 due to dementia or sarcopenia, 4 due to infection, 2 due to the patient's own decision and one each due to malignancy, fracture and sudden death (Supplementary Fig. S2, available at *Rheumatology Advances in Practice* online).

Treatment outcomes in the LORA ≥75 and LORA <75 patients

The proportion of patients with SDAI remission in the LORA ≥75 group was significantly lower than that in the LORA <75 group at week 52, and the proportion of patients with CRRP at week 52 tended to be higher in the LORA ≥75

Table 2. Treatments and implementation of T2T for LORA <75 and LORA ≥75 patients

Treatments and implementation	LORA <75 (n = 99)	LORA ≥75(n = 98)	*P*-value
MTX at week 0 (*n* = 197), %	80.8	70.4	0.089
MTX at week 52 (*n* = 184), %	85.4	70.5	0.014*
MTX at week 104 (*n* = 173), %	81.7	71.3	0.103
MTX at week 156 (*n* = 161), %	75.8	70.0	0.408
MTX dose at week 0 (*n* = 197), mg/week, mean (S.D.)	6.54 (1.52)	5.77 (1.26)	0.001*
MTX dose at week 52 (*n* = 184), mg/week, mean (S.D.)	8.93 (2.95)	7.81 (2.28)	0.011*
MTX dose at week 104 (*n* = 173), mg/week, mean (S.D.)	8.68 (3.16)	7.64 (2.35)	0.033*
MTX dose at week 156 (*n* = 161), mg/week, mean (S.D.)	8.38 (3.04)	7.50 (2.49)	0.100
Cumulative dose of MTX over 3 years, g, mean (S.D.)	6.88 (3.78)	4.78 (3.53)	<0.001*
bDMARDs at week 0 (*n* = 197), %	0.0	0.0	
bDMARDs at week 52 (*n* = 184), %	28.1	34.1	0.382
bDMARDs at week 104 (*n* = 173), %	30.1	38.8	0.232
bDMARDs at week 156 (*n* = 161), %	23.1	37.1	0.052
Number of bDMARDs over 3 years, median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.266
Number of TNF inhibitors over 3 years, %			
Median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.317
0	64.6	56.1	0.221
1	23.2	32.7	0.141
2	11.1	10.2	0.837
≥3	1.0	1.0	0.994
Abatacept use over 3 years, %	3.0	2.0	0.505
IL-6 inhibitor use over 3 years, %	4.0	5.1	0.494
GCs at week 0 (*n* = 197), %	24.2	43.9	0.004*
GCs at week 52 (*n* = 184), %	14.6	37.2	<0.001*
GCs at week 104 (*n* = 173), %	7.6	28.4	<0.001*
GCs at week 156 (*n* = 161), %	7.1	24.6	0.003*
Cumulative dose of GCs in prednisone equivalents over 3 years, g, mean (S.D.)	0.52 (1.15)	1.21 (1.63)	0.001*
Non-implementation of T2T, *n* (%)	28 (28.3)	41 (41.8)	0.046*
Patient's own decision, *n* (%)	19 (19.2)	21 (21.4)	0.696
Comorbidities/AEs, *n* (%)	11 (11.1)	27 (27.6)	0.003*
Discontinuation of observation, *n* (%)	8 (8.1)	29 (29.6)	<0.001*

* Statistically significant at $P < 0.05$.

group. At week 156, 32.7% of the LORA ≥75 and 66.7% of the LORA <75 patients achieved SDAI remission using NRI analysis ($P < 0.001$; Table 3). The proportions of patients achieving SDAI LDA and HAQ-DI ≤0.5 at weeks 52 and 156 were also significantly lower in the LORA ≥75 group (Table 3). The results were similar for only those patients who completed the 3-year observation (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). The number of swollen joints and tender joints, physician's global assessment (PhGA) and patient global assessment (PtGA) were significantly higher in the LORA ≥75 group (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). When stratified by age into four groups, the proportion of remission by NRI decreased from age 75 to 79 years and further decreased in LORA patients >80 years of age (Supplementary Table S2, available at *Rheumatology Advances in Practice* online).

SAEs in the LORA ≥75 and LORA <75 patients

Over the 3-year period, there were 40 of 98 patients with SAEs in the LORA ≥75 group and 21 of 99 patients in the LORA <75 group. The numbers of patients with each event are shown in Supplementary Table S1, available at *Rheumatology Advances in Practice* online. Serious infections were 17 in the 98 LORA ≥75 patients and 10 in the 99 LORA <75 patients. Bacterial pneumonia and *Pneumocystis* pneumonia were 5 and 4 in the 98 LORA ≥75 patients and 4 and 3 in the 99 LORA <75 patients, respectively. RA-associated interstitial lung disease and cardiovascular disease were more frequent in the LORA ≥75 patients than in LORA <75 patients. Malignancies were 6 in the LORA ≥75 patients and 5 in LORA <75 patients, and fractures were 9 in the LORA ≥75 patients and 7 in LORA <75 patients (Supplementary Table S3, available at *Rheumatology Advances in Practice* online). The cumulative incidence of any SAEs was 42.8% in the LORA ≥75 patients and 22.1% in the LORA <75 patients during the 3-year observation period. The time to occurrence of SAEs was significantly shorter in the LORA ≥75 patients (Fig. 2A). The cumulative incidence of serious infections was 19.5% in the LORA ≥75 patients and 9.4% in LORA <75 patients (not significant; Fig. 2B), while the time to events of exacerbation of extra-articular lesions (Fig. 2C) and cardiovascular events (Fig. 2E) was significantly shorter in the LORA ≥75 patients. The time

Table 3. Treatment outcomes of the LORA <75 and LORA ≥75 groups

Outcomes	LORA <75 (*n* = 99)	LORA ≥75 (*n* = 98)	*P*-value
Primary outcome			
SDAI remission at week 156, %	66.7	32.7	<0.001*
Secondary outcomes			
SDAI LDA at week 52, %	77.8	58.2	0.003*
SDAI remission at week 52, %	43.4	27.6	0.020*
HAQ-DI ≤0.5 at week 52, %	80.8	51.0	<0.001*
CRRP at week 52, %	27.1	33.0	0.385
SDAI LDA at week 156, %	88.9	61.2	<0.001*
HAQ-DI ≤0.5 at week 156, %	83.8	37.8	<0.001*

Non-responder imputation approaches were applied for estimating the rate of achievement of treatment outcomes.
* Statistically significant at $P < 0.05$.

to events of fractures (Fig. 2D) and malignancies (Fig. 2E) were not significantly different.

LORA patients ≥75 years of age were at an increased risk of not achieving SDAI remission at week 156

Several factors were more prevalent in the LORA ≥75 group than in the LORA <75 group (Table 1) and potentially related to failure to achieve remission as confounding factors. Hence sex, body weight, CRP, mTSS, HAQ, smoking history, chronic kidney disease, osteoporosis, hypertension and a history of hospitalization due to infection were included as covariates in multivariate logistic regression analysis (model 1). After adjustment, the LORA ≥75 patients had more difficulty in achieving SDAI remission than the LORA <75 patients (OR 3.20, 95% CI 1.50–6.83) (Fig. 3 and Supplementary Table S4, available at *Rheumatology Advances in Practice* online).

Because non-implementation of T2T at least once and the occurrence of SAEs over 3 years was expected to impact on failure to achieve remission, these factors were included in Model 2 as covariates. The LORA ≥75 were still more likely to have an increased risk of not achieving SDAI remission (Model 2; OR 2.82, 95% CI 1.29–6.14). The occurrence of SAEs over 3 years was also significantly associated with non-achievement of SDAI remission at week 156 (Model 2; OR 2.29, 95% CI 1.03–5.07) (Fig. 3 and Supplementary Table S4, available at *Rheumatology Advances in Practice* online), while non-implementation of T2T at least once was not (Model 2; OR 1.56, 95% CI 0.76–3.20). Even when the cumulative dose of GC, cumulative dose of MTX, and number of bDMARDs over a 3-year period were included in Model 3 as covariates, age 75 and older were significantly associated with failure to achieve remission [odds ratio 2.74 (95% CI 1.25, 6.01)] (model 3 in Fig. 3 and Supplementary Table S5, available at *Rheumatology Advances in Practice* online).

Discussion

This subanalysis of the CRANE cohort revealed the effectiveness and safety of treatment targeting LDA in LORA patients ≥75 years of age. MTX was used to a similar extent in the LORA ≥75 and LORA <75 patients as an initial treatment. GCs were used more frequently in the LORA ≥75 patients, and the frequency of adding bDMARDs to csDMARDs or switching to bDMARDs with different mechanisms of action was similar in the two groups. The cumulative incidence of SAEs over 156 weeks was significantly higher and the non-adherence to T2T due to comorbidities/AEs was more frequent in the LORA ≥75 patients. Overall, the proportion of patients achieving SDAI remission in the LORA ≥75 group was significantly lower than that in the LORA <75 group at week 156. Interestingly, age ≥75 years was associated with non-achievement of SDAI remission at week 156 after adjusting for various covariates in the multivariable analysis, including comorbidities at baseline, SAEs and non-implementation of T2T. The present study indicated that the LORA ≥75 patients were more difficult to treat than the LORA <75 patients in terms of both treatment responses and safety issues.

A recent observational study suggests that active synovitis confirmed by ultrasound-guided synovial biopsy and radiographic progression are more frequently observed in LORA compared with younger-onset RA [16]. In the current study, the LORA ≥75 patients had higher CRP levels and mTSS at baseline and more comorbidities, which were associated with poor treatment response in RA patients [11, 17–19]. Interestingly, SDAI remission was significantly less likely to be achieved for the LORA ≥75 patients after adjusting for these factors at baseline, SAEs and failure to implement T2T. Disease susceptibility genes were associated with joint destruction in younger-onset RA (≤40 years), but not in middle- or late-onset RA [20]. There may be unidentified exacerbating factors in older-age onset. Age ≥65 years has been shown not to be associated with response to treatment with bDMARDs or Janus kinase (JAK) inhibitors in the post hoc analysis of RCTs [4–7, 21, 22]. Although the results differ from those of our study, few patients recruited into the RCTs were >75 years of age. It is possible that age-related alterations in the immune system may affect the pathogenesis of LORA in patients >75 years of age [23].

The PtGA has been reported to be comparable between LORA and young-onset RA in the evaluation of effectiveness during the first year of treatment [24, 25]. However, in assessing the long-term effectiveness in RA, PtGA may increase with age [25–27]. In the present study, the numbers of swollen joints and tender joints, PhGA and PtGA were involved in the difference in the proportion of achieving remission at week 156. Especially compared with LORA <75 patients, LORA ≥75 patients showed poorer improvement in PtGA from 52 to 156 weeks (Supplementary Table S1, available at *Rheumatology Advances in Practice* online), which may be implicated in the lower proportion of achieving remission at week 156 week in LORA ≥75 patients.

The efficacy of MTX plus TNFi or MTX plus JAK inhibitor as initial therapy for older patients has been shown in RCT subanalyses [3–7, 22]. The disadvantage of TNFi monotherapy compared with TNFi plus MTX was demonstrated in patients ≥65 years of age [4, 28]. However, this may not be the case for LORA patients >75 years of age. The disadvantage of TNFi monotherapy compared with TNFi plus MTX on drug retention rate was not observed in patients ≥75 years of age in the BSR Biologics Register [29]. In the present study, TNFi were used in the same proportion and TNFi was added to MTX in most cases of MTX failures in both groups. Therefore, the effectiveness and safety of the TNFi plus MTX could not be compared with those of TNFi monotherapy. However, about 60% of patients had MTX-associated AEs in the CRANE cohort [12], and the time to discontinue MTX was significantly shorter in the LORA ≥75 patients than in the LORA <75 patients in the present analysis (Supplementary Fig. S1A, available at *Rheumatology Advances in Practice* online). It is necessary to investigate in clinical trials whether it is better to discontinue or continue MTX in patients >75 years of age who have achieved remission or LDA with combination therapy with MTX and a bDMARD or JAK inhibiter.

A definition of difficult-to-treat (D2T) RA has been proposed, which includes failure to achieve therapeutic goals with two or more molecular-targeted agents with different mechanisms of action [30]. Discontinuation due to safety issues, limited drug options because of AEs and multiple comorbidities were associated with D2T [31, 32]. A pitfall of the D2T definition is the presence of older patients who cannot use multiple bDMARDs with different mechanisms of action because of comorbidities and AEs. A previous study

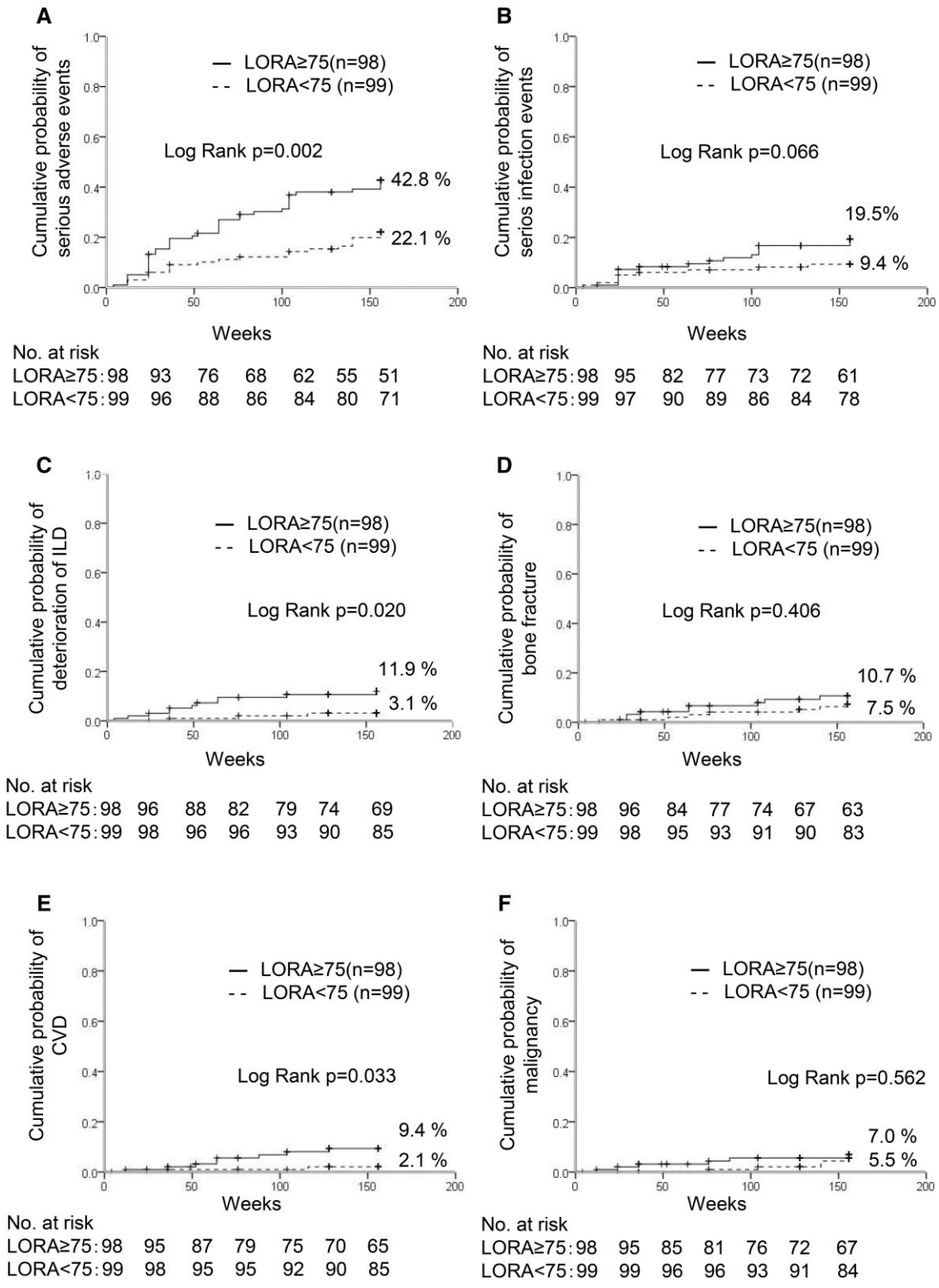

Figure 2. Cumulative rates of SAEs, SIEs, deterioration of ILD and bone fracture. SAEs of interest were collected, including SIEs, deterioration of ILD, bone fractures, CVDs and malignancy. The cumulative rate of **(A)** SAEs, **(B)** SIEs, **(C)** deterioration of ILD and **(D)** bone fracture for the LORA ≥75 and LORA <75 groups were analysed using the Kaplan–Meier method. SIEs: serious infectious events; CVDs: cardiovascular diseases

reported that some older patients with multiple comorbidities do not achieve their treatment goals despite not meeting the definition of D2T [33]. The present study also suggested SAEs during T2T and non-adherence to T2T due to comorbidities/AEs were more frequently observed in the LORA ≥75 group than in the LORA <75 group. Although only a small number of patients in this study met the definition of D2T, the proportion of patients who fail to achieve remission or LDA was higher in the LORA ≥75 group. This suggests that, in addition to D2T RA, LORA patients >75 years of

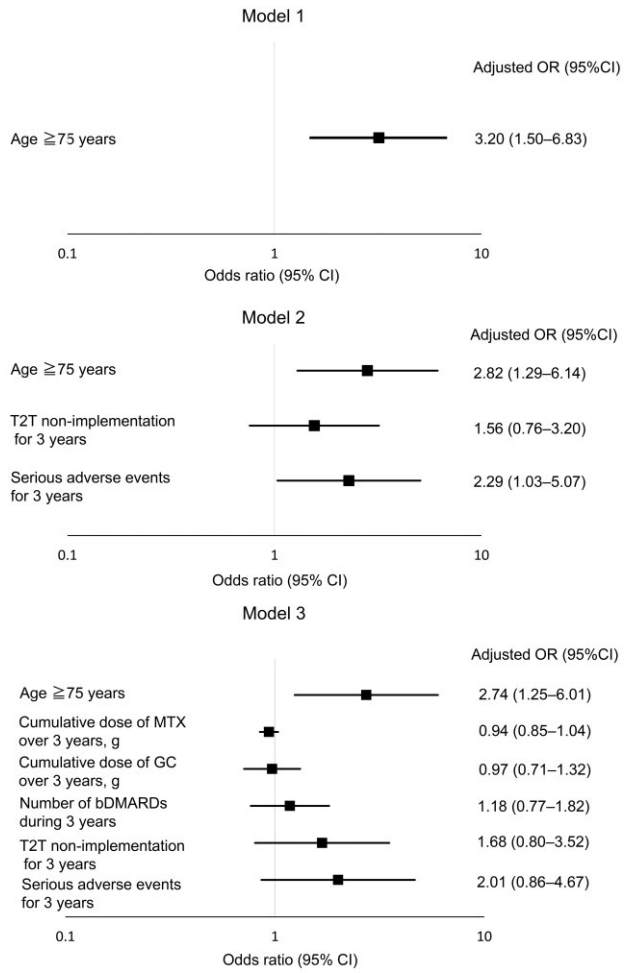

Figure 3. Association between LORA ≥75 and failure to achieve remission. Multivariate logistic regression analysis was performed with sex, body weight, CRP, mTSS, HAQ, smoking history, CKD, osteoporosis, hypertension and history of hospitalized infection as covariates in model 1. In model 2, non-implementation of T2T at least once and the occurrence of SAEs over 3 years was added to model 1 and analysed. In model 3, the cumulative dose of GCs, cumulative dose of MTX and number of bDMARDs over 3 years were added to model 2. CKD: chronic kidney disease

age should be recognized as a population less likely to achieve treatment goals.

Age, chronic lung disease and GC use were reported as risk factors of serious infections in non-elderly RA [34, 35]. Our previous report on the CRANE cohort indicated that factors associated with the occurrence of SAEs during T2T were chronic lung disease at baseline, a history of malignancy and poor control of disease activity [12]. Other studies also found that an increase in SAEs in patients with RA was associated with poor control of disease activity [36, 37]. Because there was no difference in the proportion of baseline lung disease and malignancy between the two groups in the present study, the poor control of disease activity might be a factor associated with the increased incidence of SAEs in the LORA ≥75 group.

The association of age with the occurrence of serious infections under bDMARDs has been documented in multicentre studies and post-marketing surveillance in Japan [38–43], and in a meta-analysis as well [3]. In the present study, the frequency of serious infections was not significantly different between the two groups. A similar incidence of serious infections in the LORA ≥75 and LORA <75 groups has also been reported in other studies [44–46]. Prognosis studies reported that the relative risk of serious infection under bDMARDs compared with csDMARDs was not elevated in RA patients ≥75 years of age [47, 48]. These findings suggest that the T2T strategy, including bDMARDs, was considered acceptable in terms of safety in patients >75 years of age.

Some limitations of this study need to be mentioned. First, it is a single-centre cohort study with a small sample size, which may limit the generalizability of this study. Second, this study was conducted on patients treated between 2008 and 2015 and a TNFi was used as a first bDMARD for patients with inadequate response to MTX. In some cases, bDMARDs were switched from a TNFi to another TNFi, which may have affected treatment outcomes. Third, 29.6% of the LORA ≥75 patients discontinued the observation within the 3-year period. Since patients who were no longer able to attend outpatient clinics due to AEs or received an increased dose of GCs for worsening ILD were censored at the onset of the AE or the dose escalation of GC, we might have underestimated the actual number of deaths due to SAEs or ILD.

In conclusion, LORA ≥75 patients were different from LORA <75 patients in terms of both effectiveness and safety of treatment. The poorer treatment response and higher incidence of SAEs made it challenging to achieve remission in the LORA ≥75 patients with MTX-naïve LORA. Optimal treatment strategies for LORA ≥75 patients should be addressed in the near future.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

All the data supporting the conclusions of this article are included within the article.

Authors' contributions

T.M., T.S., and M.H. were responsible for conception and design, data collection and analysis, critical revision, and manuscript writing. T.M., T.S. and T.I. were responsible for statistical analysis. T.H., K.K., M.K., H.B., M.T., and F.H. were responsible for data collection, analysis, and critical revision. M.K. and N.M. were responsible for conception and design, and critical revision. All authors read and approved the final manuscript.

Funding

This work was supported by the Ministry of Education, Culture, Sports, Science and Technology (Grant-in-Aid for Scientific Research 26461480), the Ministry of Health, Labour and Welfare, Japan (22FE0201) and the Japan Agency for Medical Research and Development (21ek0410086h0001).

Disclosure statement: T.S. has received research grants from Asahi Kasei, Daiichi Sankyo, Chugai Pharmaceutical and Ono Pharmaceutical and honoraria from AbbVie Japan, Asahi Kasei, Astellas Pharma, Ayumi Pharmaceutical, Bristol

Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Mitsubishi-Tanabe Pharma, Ono Pharmaceutical, Pfizer Japan, Taisho Pharmaceutical, Takeda Pharmaceutical and UCB Japan. K.K. has received research grants from Asahi Kasei and speaker bureau fees from Bristol Myers Squibb, Chugai Pharmaceutical, Astellas Pharma, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Boehringer Ingelheim, AbbVie/Abbott, Asahi Kasei, Pfizer, Nippon Shinyaku, Eisai and Taisho Pharmaceutical. F.H. has received honoraria from Janssen Pharmaceuticals, Ono Pharmaceuticals and Mitsubishi Tanabe Pharma. M.Ko. has received speaker bureau fees from AbbVie, Astellas, Ayumi Pharma, Chugai, Eisai, Eli Lilly, Janssen, Ono Pharmaceutical, Pfizer, Mitsubishi Tanabe Pharma and Takeda Pharmaceutical. M. H. has received research grants from AbbVie Japan, Asahi Kasei, Astellas Pharma, Ayumi Pharmaceutical, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Kissei Pharmaceutical, Mitsubishi Tanabe Pharma, Nippon Kayaku, Sekiui Medical, Shionogi & Co., Taisho Pharmaceutical, Takeda Pharmaceutical and Teijin Pharma; speaker fees from AbbVie Japan, Ayumi Pharmaceutical, Boehringer Ingelheim Japan, Bristol Myers Squibb, Chugai Pharmaceutical, Eisai, Eli Lilly Japan, GlaxoSmithKline, Kissei Pharmaceutical, Pfizer Japan, Takeda Pharmaceutical and Teijin Pharma and is a consultant for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Kissei Pharmaceutical and Teijin Pharma. All other authors have declared no conflicts of interest. The sponsors were not involved in the study design; in the collection, analysis and interpretation of data; in the writing of this manuscript or in the decision to submit the article for publication.

Acknowledgements

The authors would like to acknowledge the following investigators: Waka Yokoyama, Takeshi Kusuda, Marina Tsuchida and Yoji Komiya of the Tokyo Metropolitan Geriatric Hospital for collecting the data on comorbidities and SAEs; and Hideki Ito, Atsushi Araki, Kazumasa Harada and Shunei Kyo of the Tokyo Metropolitan Geriatric Hospital for advice about geriatric medicine.

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