Factors associated with normal physical function in patients with rheumatoid arthritis of different ages

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Abstract

Background

To investigate factors associated with normal physical function of middle-aged (55-64), old (65-74) or very old (75-84) patients with rheumatoid arthritis (RA).

Methods

Data from RA patients in the National Database of Rheumatic Diseases in Japan (NinJa) were extracted from April 2017 to March 2018. Factors associated with impaired physical function (Health Assessment Questionnaire Disability Index [HAQ-DI] >0.5) were analyzed by multivariable logistic regression. Association of glucocorticoids (GCs) and age with impaired physical function were presented as adjusted odds ratio (OR) for the 5 groups relative to middle-aged patients without GCs as the reference group.

Results

Low disease activity (3.3< simplified disease activity index [SDAI] ≤11) or remission (SDAI ≤3.3) was achieved in 3,466 (31.4%) or 3,021(27.4%) of 11,036 patients aged 55-84, respectively. To reduce the influence of joint destruction on HAQ-DI, we assessed the 3,708 patients in both SDAI ≤11 and Steinbrocker stage I/II. About half of the very old patients were receiving methotrexate, which was the lowest proportion amongst the three age groups. GCs were continued in 32.6% of very old patients, and the proportion was higher than in old and middle-aged patients. On the other hand, 16.2% of the very old patients received biological disease-modifying anti-rheumatic drugs (bDMARDs), and the proportions were similar among the three groups. SDAI was higher in patients with HAQ-DI >0.5 at all ages, and GCs was used more frequently in the old and very old patients with HAQ-DI >0.5, compared to those with HAQ-DI ≤0.5. To minimize the influence of disease activity on HAQ-DI, we selected the 2078 patients in both remission and stage I/II. Multivariable analysis revealed the use of GCs further increased the adjusted OR from 4.01 (95% confidence interval [CI] 2.30-6.99) to 6.81 (95%CI 3.65-12.7) in the very old patients, while the adjusted OR was 2.03 (95%CI 1.17-1.13) in the old patients without GCs, 2.22 (95%CI 1.13-4.36) in the old patients with GCs, and 0.73 (95%CI 0.21-2.56) in the middle-aged patients with GCs.

Conclusions

The negative impact of GCs was likely to most strongly influence physical function of very old patients than middle-aged or old patients.

Background

Achieving remission or low disease activity (LDA) has become a realistic goal in rheumatoid arthritis (RA) with the evolution of treat-to-target (T2T) strategies using conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as methotrexate (MTX), biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs). Abrogation of inflammation and prevention of joint destruction were associated with physical function in patients with RA (1−3).

The increasing age of onset of RA in Japan and its increasing incidence in old patients has been noted (4, 5). Old patients given bDMARDs or tsDMARDs achieved favorable outcomes (6–9), but had lower rate of achievement of clinical remission and more serious infectious events or serious adverse events than younger patients (10). Older patients have higher disease activity and a higher frequency of comorbidities than younger patients, and it was associated with poorer treatment response and functional disability (11, 12). It was challenging to implement T2T achieving remission in frail older patients with comorbidities (13). Therefore, drug use may differ among patients who achieved remission or LDA, according to whether they are middle-aged, old or very old.

Previous cohort studies showed that glucocorticoids (GCs) were more frequently given to older RA patients who received bDMARDs less often (14, 15). Long-standing use of GCs was associated with serious infectious events (16–18), cardiovascular events (19, 20), and fracture (21).

The normalization of physical functioning is an important therapeutic goal for old patients with RA, because physical deterioration in old adults is associated with progression of physical frailty and subsequently decreased life expectancy (22). We hypothesized that drugs used and factors associated with the normal physical function may differ depending on age, from middle-age to old and very old age, even when disease activity is controlled to similar degrees (LDA or remission). Especially, GC use might have greater impact on physical function in very old patients or old patients, compared to middle-aged patients.

Using a large national registry of Japanese RA patients, we utilized the Health Assessment Questionnaire Disability Index (HAQ-DI) as an indicator of normal physical function and investigated current status of treatment for middle-aged, old, and very old patients with RA who had achieved LDA or remission, based on the Simplified Disease Activity Index (SDAI). We also assessed whether association with normal physical function and GCs were different in middle-aged, old or very old RA patients.

Methods

NinJa registry

The National Database of Rheumatic Diseases in Japan (NinJa) is a nationwide, multicenter, prevalent, longitudinal observational database of RA patients (16 years of age or older) treated in Japan with a fixed data collection interval of 1 year (23). The NinJa registry was established in 2002 and currently collects information annually from 49 institutions located throughout Japan. The registry, and all subsequent studies utilizing pre-existing registry data, was approved by the Sagamihara National Hospital Institutional Review Board.

For the present study, we used data from the NinJa registry originating from the time period April 2017 to March 2018. The database included age, sex, duration of disease, SDAI, anti-citrullinated protein antibody (ACPA), medications (MTX, csDMARDs other than MTX, bDMARDs, tsDMARDs, GCs, non-steroidal anti-inflammatory drugs [NSAIDs]), HAQ-DI, EuroQol 5 Dimension (EQ-5D) (24), C-reactive protein (CRP), body mass index (BMI), serum creatinine (Cr), complications requiring hospitalization (all hospitalizations, infectious disease, interstitial lung disease, cerebrovascular disease, cardiac disease), and malignancies during the 1-year observation period. In NinJa registry, evaluation of radiographic joint destruction was done with Steinbrocker stage (25) at hand and wrist.

Outcomes

The primary outcome of the present analysis is the normal physical function (defined as a HAQ-DI ≤0.5). SDAI disease activity states were defined as follows: SDAI remission (SDAI≦3.3); SDAI LDA (3.3<SDAI≦11).

Statistical Methods

One-way analysis of variance, the Kruskal–Wallis test, and the Chi-squared test were used to compare clinical findings among middle-aged, old, and very old patients. For comparisons of the clinical findings between patients with HAQ-DI >0.5 or ≤0.5, and between patients with or without GC, student's t test, the Mann-Whitney test, and the Chi-squared test were used depending on their distribution. To examine associations between HAQ-DI >0.5 and GCs use in middle-aged, old, and very old patients, we stratified the patients aged 55-84 into six groups, namely very old, old and middle-aged patients with or without GCs. Adjusted odds ratios (ORs) of 5 groups relative to the reference group of middle-aged patients without GCs were calculated in the multivariable logistic regression analysis. The reported p values were two-tailed, and the level of significance was set at p <0.05. All analytical procedures were performed using IBM SPSS Version 27.

Results

Baseline characteristics of old patients achieving LDA in the NinJa cohort

Of the 15,185 patients enrolled in the NinJa database in 2017, 9,387(61.8%) were ≥65 years of age, with 5,227 included as an old group aged 65-74 years, and 3,460 as a very old group of 75-84 years. A middle-aged group (n=2,986) at 55-64 years was selected to act as the reference control cohort for the old patients. Overall, 11,849 patients aged 55-84 years were selected of whom data on SDAI could be extracted for 11,036. SDAI LDA or SDAI remission was achieved in 3,466 (31.4%) or 3,021(27.4%) of these 11,036, respectively. Of the total of 6,487 patients whose disease activity was LDA or remission, 3,708 were in stage I/II according to the Steinbrocker classification, and 2,778 in stage III/IV (Table 1).

	Stage I/II				Stage III/IV			
	55-64 years (n=1,107)	65-74 years (n=1,648)	75-84 years (n=953)	*P* value	55-64 years (n=612)	65-74 years (n=1,320)	75-84 years (n=846)	*P* value
Age, year, mean (S.D.)	60.0 (2.9)	69.4 (2.8)	78.6 (2.7)	<0.001	60.5 (2.6)	69.5 (2.8)	78.5 (2.7)	<0.001
Duration of disease, year, median (IQR)	6 (3-10)	7 (3-11)	7 (3-12)	0.028	17 (12-26)	21 (13-30)	24 (14-33)	<0.001
Gender, female, %	75.1	69.8	70.4	0.006	86.9	85.6	84.5	0.438
BMI, mean (S.D.)	22.7 (3.7)	22.7 (3.5)	22.3 (3.3)	0.016	21.7 (3.6)	21.9 (3.5)	21.8 (3.5)	0.462
ACPA positive, %	68.2	64.7	56.1	<0.001	85.5	86.7	79.8	0.054
Tender joint count, median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.073	0 (0-2)	0 (0-1)	0 (0-1)	0.075
Swollen joint count, median (IQR)	0 (0-0)	0 (0-0)	0 (0-1)	0.751	0 (0-1)	0 (0-1)	0 (0-1)	0.116
Patient VAS, 0-10 cm, median (IQR)	1.0 (0.3-2.1)	1.0 (0.3-2.8)	1.3 (0.5-2.7)	<0.001	1.6 (0.6-3.0)	1.6 (0.7-3.0)	2.3 (1.0-4.2)	<0.001
Physician VAS, 0-10 cm, median (IQR)	0.7 (0.2-1.2)	0.6 (0.2-1.1)	0.7 (0.3-1.2)	0.431	1 (0.5-1.6)	1.0 (0.5-1.6)	1.0 (0.5-1.6)	0.975
CRP, mg/dL, median (IQR)	0.10 (0.05-0.28)	0.12 (0.06-0.30)	0.14 (0.06-0.38)	<0.001	0.14 (0.06-0.40)	0.17 (0.06-0.47)	0.19 (0.07-0.53)	0.002
SDAI, median (IQR)	2.83 (1.07-5.38)	2.58 (1.09-5.17)	3.00 (1.36-6.04)	<0.001	4.90 (2.33-7.52)	4.56 (2.26-7.33)	5.32 (2.99-7.91)	<0.001
HAQ-DI, median (IQR)	0 (0-0.25)	0 (0-0.35)	0.25 (0-0.75)	<0.001	0.38 (0-1.00)	0.44 (0.1.13)	0.88 (0.25-1.75)	<0.001
EQ-5D, mean (S.D.)	0.86 (0.16)	0.85 (1.7)	0.78 (0.18)	<0.001	0.77 (0.19)	0.75 (0.19)	0.68 (0.21)	<0.001

ACPA: anti-citrullinated protein antibody, bDMARDs: biological disease-modifying anti-rheumatic drugs (DMARDs), BMI: body mass index, BUC: bucillamine, Cr: creatinine, CRP: C-reactive protein, EQ-5D: EuroQol 5 dimension, GCs: glucocorticoids, HAQ-DI: health assessment questionnaire-disability index, Interstitial lung disease: ILD, IGR: iguratimod, IQR: interquartile range, LDA: low disease activity, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, SASP: salazosulfapyridine, S.D: standard deviation, SDAI: simplified disease activity index, TAC: tacrolimus, TNFi: TNF inhibitor, tsDMARDs: targeted synthetic DMARDs, VAS: visual analogue scale.

	Stage I/II				Stage III/IV			
Serum Cr, mg/dl, median (IQR)	0.66 (0.57-0.76)	0.68 (0.58-0.81)	0.72 (0.60-0.86)	<0.001	0.61 (0.54-0.71)	0.63 (0.55-0.75)	0.69 (0.60-0.83)	<0.001
NSAIDs, %	31.6	30.7	29.0	0.418	45.9	39.0	39.3	0.01
MTX, %	74.1	67.1	52.5	<0.001	73.5	68.3	54.7	<0.0016
bDMARDs, %	19.8	17.6	16.2	0.093	35.3	32.7	29.5	0.061
TNFi, %	10.7	9.1	7.5	0.035	18.3	18.6	12.6	0.001
tsDMARDs, %	1.8	1.8	0.9	0.159	2.6	3.2	1.7	0.092
GCs, %	20.8	25.4	32.6	<0.001	33.7	35.2	45.2	<0.001
SASP, %	19.1	20.1	25.4	0.002	17.0	17.4	17.9	0.891
TAC, %	8.2	9.9	12.9	0.002	10.1	11.7	16.1	0.001
BUC, %	7.8	10.3	12.9	0.001	10.5	9.2	9.7	0.701
IGR, %	7.6	6.3	7.5	0.315	7.8	6.4	7.4	0.42
All hospitalization, %	3.9	7.0	10.5	<0.001	10.9	10.2	14.2	0.015
Infectious disease Hospitalization, %	0.5	1.6	2.5	0.001	2.6	2.5	5.4	0.001
Osteoporosis hospitalization, %	0.2	0.5	1.1	0.011	0.5	1.5	2.5	0.011
Cardiac disease hospitalization, %	0.2	0.4	0.3	0.542	0.2	0.1	0.7	0.022
ILD, % hospitalization, %	0.2	0.5	0.6	0.272	0.3	0.1	0.4	0.316
Cerebrovascular disease hospitalization, %	0.0	0.5	0.6	0.043	0.0	0.3	0.6	0.144
Malignancy, %	0.6	1.6	1.6	0.056	0.5	0.8	1.3	0.256

ACPA: anti-citrullinated protein antibody, bDMARDs: biological disease-modifying anti-rheumatic drugs (DMARDs), BMI: body mass index, BUC: bucillamine, Cr: creatinine, CRP: C-reactive protein, EQ-5D: EuroQol 5 dimension, GCs: glucocorticoids, HAQ-DI: health assessment questionnaire-disability index, Interstitial lung disease: ILD, IGR: iguratimod, IQR: interquartile range, LDA: low disease activity, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, SASP: salazosulfapyridine, S.D: standard deviation, SDAI: simplified disease activity index, TAC: tacrolimus, TNFi: TNF inhibitor, tsDMARDs: targeted synthetic DMARDs, VAS: visual analogue scale.

In stage I/II patients, ACPA positivity decreased with age, and higher HAQ-DI and lower EQ-5D were observed in the very old patients. About half of the very old patients were receiving MTX, which was the lowest proportion amongst the three age groups. GCs were continued in 32.6% of very old patients, and the proportion was higher than in old and middle-aged patients. On the other hand, 16.2% of the very old patients received bDMARDs, and the proportion was comparable to that in middle aged and old patients. The proportion of MTX use in cases of concomitant bDMARDs use was 66.4%

in middle-aged patients and 59.6% in the old but only 43.3% in very old patients. Newly-developed comorbidities and infections requiring hospitalization increased with age (Table 1).

Patients with stage III/IV had longer disease duration, higher proportion of ACPA positivity, higher HAQ-DI and lower EQ-5D than patients with stage I/II. The differences in the SDAI, HAQ-DI, EQ-5d, and proportion of each drug use among the three age groups tended to be the same as the results observed in the patients with stage I/II (Table1).

Clinical features of patients with and without normal physical function when achieving LDA or remission at stage I/II

To reduce the influence of progression of joint destruction on physical function, we assessed the 3,708 patients in stage I/II whose disease activity was SDAI ≤11 (SDAI LDA or remission). Impaired physical function (HAQ-DI >0.5) was reported for 646 (17.6%) of these 3,708 patients. The patients with impaired physical function had higher SDAI, more tender joints, higher patient VAS, and higher physician VAS than those with normal physical function (HAQ-DI ≤0.5), even after achieving LDA or remission. On the other hand, the number of swollen joints was comparable in patients with or without impaired physical function. These results were the same for all three age groups (Table 2).

Table 2
Characteristics of each age groups of the patients in both SDAI ≤11 (SDAI LDA or remission) and stage I/II with normal physical function and those without.

	55-64 years			65-74 years			75-84 years		
	HAQ ≦0.5 (n=991)	HAQ >0.5 (n=116)	P Value	HAQ ≦0.5 (n=1,409)	HAQ >0.5 (n=239)	P value	HAQ ≦0.5 (n=662)	HAQ >0.5 (n=291)	P value
Age, year, mean (S.D.)	60.0 (2.9)	60.0 (3.0)	0.153	69.3 (2.8)	70.0 (2.9)	0.001	78.3 (2.6)	79.5 (2.8)	<0.001
Duration of disease, year, median, (IQR)	6 (3-10)	7 (3-13)	0.879	7 (3-11)	10 (5-16)	0.038	7 (4-14)	8 (4-13)	0.374
Gender, female, %	73.6	88.8	<0.001	68.1	80.0	<0.001	68.4	74.9	0.025
BMI, mean (S.D.)	22.6. (3.6)	23.5 (4.5)	0.025	22.7 (3.4)	22.7 (4.0)	0.999	22.3 (3.1)	22.4 (3.7)	0.569
ACPA positive, %	69.0	60.8	0.268	64.6	65.2	1.000	53.7	61.9	0.107
Tender joint count, median (IQR)	0 (0-1)	1 (0-2)	<0.001	0 (0-0)	0 (0-1)	<0.001	0 (0-1)	0 (0-1)	<0.001
Swollen joint count, median (IQR)	0 (0-0)	0 (0-1)	0.100	0 (0-0)	0 (0-1)	0.554	0 (0-0)	0 (0-1)	0.655
Patient VAS, 0-10 cm, median (IQR)	0.9 (0.3-2.0)	2.9 (1.7-4.5)	<0.001	0.8 (0.2-1.9)	2.7 (1.2-4.2)	<0.001	0.9 (0.3-2.0)	2.4 (1.1-4.5)	<0.001
Physician VAS, 0-10 cm, median (IQR)	0.6 (0.2-1.1)	1.1 (0.7-1.8)	<0.001	0.6 (0.2-1.0)	1.0 (0.5-1.6)	<0.001	0.6 (0.2-1.0)	1.0 (0.5-1.6)	<0.001
CRP, mg/dl, median (IQR)	0.1 (0.05-0.28)	0.12 (0.06-0.39)	0.068	0.12 (0.05-0.30)	0.13 (0.06-0.30)	0.339	0.11 (0.05-0.33)	0.20 (0.07-0.52)	<0.001

ACPA: anti-citrullinated protein antibody, bDMARDs: biological disease-modifying anti-rheumatic drugs (DMARDs), BMI: body mass index, Cr: creatinine, CRP: C-reactive protein, GCs: glucocorticoids, HAQ-DI: health assessment questionnaire-disability index, IQR: interquartile range, LDA: low disease activity, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, S.D: standard deviation, SDAI: simplified disease activity index, TNFi: TNF inhibitor, tsDMARDs: targeted synthetic DMARDs, VAS: visual analogue scale.

	55-64 years			65-74 years			75-84 years		
SDAI, median (IQR)	2.47	5.78	<0.001	2.29	5.41	<0.001	2.35	5.63	<0.001
	(1.02-5.00)	(3.92-8.24)		(0.97-4.66)	(2.80-7.80)		(1.11-4.82)	(2.70-8.24)	
SDAI remission, %	59.6%	19.0%	<0.001	62.5%	30.1%	<0.001	64.0%	30.6%	<0.001
Serum Cr, mg/dl, median (IQR)	0.66	0.61	0.056	0.69	0.66	0.007	0.71	0.72	0.79
	(0.57-0.77)	(0.54-0.75)		(0.59-0.81)	(0.53-078)		(0.61-0.86)	(0.58-0.89)	
NSAIDs, %	29.9	46.6	<0.001	29.5	38.1	0.005	26.0	35.7	0.002
MTX, %	64.6	69.8	0.265	67.6	64.4	0.372	59.2	37.1	<0.001
bDMARDs, %	19.3	24.1	0.219	16.6	23.4	0.008	13.9	21.3	0.003
TNFi, %	10.9	9.5	0.752	9.1	9.2	0.904	7.4	7.6	1.000
tsDMARDs, %	1.5	4.3	0.05	1.6	3.3	0.115	1.1	0.7	0.730
GCs, %	20.0	27.6	0.069	23.9	34.3	0.001	26.9	45.7	<0.001
All hospitalization, %	0.3	0.9	0.01	6.1	12.6	0.001	7.9	16.5	<0.001
Infectious disease hospitalization, %	0.1	0.0	-	1.1	4.2	0.002	1.4	5.2	0.001

ACPA: anti-citrullinated protein antibody, bDMARDs: biological disease-modifying anti-rheumatic drugs (DMARDs), BMI: body mass index, Cr: creatinine, CRP: C-reactive protein, GCs: glucocorticoids, HAQ-DI: health assessment questionnaire-disability index, IQR: interquartile range, LDA: low disease activity, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, S.D: standard deviation, SDAI: simplified disease activity index, TNFi: TNF inhibitor, tsDMARDs: targeted synthetic DMARDs, VAS: visual analogue scale.

Regarding the proportion of use of medications in patients with or without impaired physical function, MTX was used less frequently in very old patients with impaired physical function. GCs were given more frequently to those old and very old patients with impaired physical function, while the proportion of GCs use in middle-aged patients was similar regardless of physical function (Table 2). The proportion of patients with newly-developing infectious diseases requiring hospitalization in those who had impaired physical function was significantly higher than those without impaired function in the old and very old age groups. Serum Cr was almost similar between patients with or without impaired physical function in all three age groups (Table 2).

Characteristics of each age groups of the patients at stage I/II taking GCs or not

In patients in SDAI ≤11, patients with GCs had higher SDAI, higher HAQ-DI, and more newly-developing comorbidities than those without GCs in all three age groups (Table 3). Interestingly, in very old patients in SDAI ≤3.3, even though SDAI was similar between patients with and without GCs, HAQ-DI was higher in patients with GCs than those without GCs. In contrast, in middle-aged patients in SDAI ≤3.3, even though SDAI was higher in patients with GCs than in those without GCs, HAQ-DI was similar between patients with and without GCs. In old patients in SDAI ≤3.3, both SDAI and HAQ-DI was higher in patients with GCs than in those without GCs (Table 3). Regardless of age or remission status, the

proportions of bDMARD use were similar between patients with and without GCs. MTX was less used in patients with GCs than those without GCs in the middle-aged and old patients, but the proportion of MTX use was similar between very old patients in SDAI remission. Newly-developing comorbidities were more frequently reported in patients with GCs than those without GCs in all three age groups, except for old patients in remission (Table 3).

Table 3
Characteristics of groups of patients in stage I/II with glucocorticoid or not.

	Patients in SDAI ≤11			Patients in SDAI ≤3.3		
	Without GCs	With GCs	*P* value	Without GCs	With GCs	*P* value
75-84 years old	n=642	n=311		n=371	n=142	
Age, year, mean (S.D.)	78.4 (2.7)	79.0 (2.8)	0.004	78.4 (2.7)	78.7 (2.8)	0.266
Duration of disease, year, median (IQR)	8 (4-14)	6 (3-12)	0.064	8.5 (4-14)	5 (2-9)	0.001
Gender, female, %	72.2	66.6	0.082	70.6	64.8	0.203
BMI, mean (S.D.)	22.3 (3.2)	22.4 (3.5)	0.684	22.3 (3.1)	22.6 (3.2)	0.463
ACPA positive, %	54.6	58.8	0.390	51.8	54.4	0.789
SDAI, median (IQR)	2.82 (1.32-5.60)	3.75 (1.66-7.54)	<0.001	1.45 (0.74-2.35)	1.56 (1.14-2.24)	0.267
HAQ-DI, median (IQR)	0.13 (0-0.50)	0.38 (0.00-1.13)	<0.001	0.00 (0.00-0.25)	0.12 (0.00-0.63)	0.003
Serum Cr mg/dl, median (IQR)	0.70 (0.60-0.85)	0.75 (0.61-0.90)	0.076	0.72 (0.60-0.86)	0.71 (0.59-0.87)	0.849
NSAIDs, %	24.9	37.3	<0.001	19.4	35.9	<0.001
MTX, %	56.4	44.4	0.001	55.5	49.3	0.235
bDMARDs, %	16.4	15.8	0.851	16.7	16.2	1.000
All hospitalization, %	7.5	16.7	<0.001	5.6	12.7	0.014
Infectious disease hospitalization, %	1.4	4.8	0.003	0.8	2.8	0.096
65-74 years old	n=1229	n=419		n=757	n=195	
Age, year, mean (S.D.)	69.4 (2.8)	69.5 (2.7)	0.811	69.3 (2.8)	69.5 (2.8)	0.416
Duration of disease, year, median (IQR)	7 (4-12)	7 (3-13)	0.391	8 (4-13)	7 (3-13)	0.915
Gender, female, %	71.1	65.9	0.049	70.0	64.1	0.119
BMI, mean (S.D.)	22.7 (3.4)	22.5 (3.5)	0.192	22.7 (3.4)	22.6 (3.6)	0.522
ACPA positive, %	65.4	62.8	0.503	64.8	59.4	0.347
SDAI, median (IQR)	2.45 (1.02-44.81)	3.59 (1.88-6.17)	<0.001	1.30 (0.55-2.18)	1.76 (1.05-2.37)	<0.001
HAQ-DI, median (IQR)	0.00 (0.00-0.25)	0.13 (0.00-0.38)	<0.001	0.00 (0.00-0.13)	0.00 (0.00-0.25)	0.001

ACPA: anti-citrullinated protein antibody, bDMARDs: biological disease-modifying anti-rheumatic drugs (DMARDs), BMI: body mass index, Cr: creatinine, GCs: glucocorticoids, HAQ-DI: health assessment questionnaire-disability index, IQR: interquartile range, LDA: low disease activity, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, S.D: standard deviation, SDAI: simplified disease activity index.

	Patients in SDAI ≤11			Patients in SDAI ≤3.3		
Serum Cr mg/dl, median (IQR)	0.68 (0.58-0.79)	0.70 (0.58-0.84)	0.115	0.69 (0.59-0.81)	0.69 (0.57-0.88)	0.639
NSAIDs, %	26.9	41.8	<0.001	21.1	38.5	<0.001
MTX, %	70.4	57.5	<0.001	69.7	53.3	<0.001
bDMARDs, %	18.2	15.8	0.266	18.6	18.5	1.000
All hospitalization, %	6.0	10.0	0.008	5.9	7.7	0.408
Infectious disease hospitalization, %	1.1	2.9	0.021	0.8	2.6	0.054
55-64 years old	n=877	n=230		n=528	n=85	
Age, year, mean (S.D.)	59.9 (2.8)	60.0 (2.9)	0.479	60.0 (2.9)	60.1 (3.0)	0.722
Duration of disease, year, median (IQR)	6 (3-10)	7 (3-13)	0.024	7 (4-11)	8 (3-13)	0.259
Gender, female, %	76.6	69.6	0.032	77.3	61.2	0.003
BMI, mean (S.D.)	22.5 (3.6)	23.3 (4.3)	0.010	22.5 (3.4)	23.1 (4.5)	0.119
ACPA positive, %	66.7	74.1	0.164	67.1	76.7	0.221
SDAI, median (IQR)	2.60 (0.93-4.87)	4.6 (2.30-7.52)	<0.001	1.12 (0.4-1.94)	1.73 (0.90-2.55)	0.001
HAQ-DI, median (IQR)	0.00 (0.00-0.13)	0.00 (0.00-0.38)	0.001	0.00 (0.00-0.00)	0.00 (0.00-0.13)	0.231
Serum Cr mg/dl, median (IQR)	0.64 (0.56-0.74)	0.68 (0.58-0.80)	0.005	0.65 (0.56-0.74)	0.71 (0.61-0.83)	0.006
NSAIDs, %	27.9	45.7	<0.001	20.8	37.6	0.001
MTX, %	77.0	63.0	<0.001	78.2	57.6	<0.001
bDMARDs, %	19.2	22.2	0.307	20.8	24.7	0.476
All hospitalization, %	3.1	7.0	0.011	1.9	7.1	0.015
Infectious disease hospitalization, %	0.1	2.1	0.002	0	3.5	0.003

ACPA: anti-citrullinated protein antibody, bDMARDs: biological disease-modifying anti-rheumatic drugs (DMARDs), BMI: body mass index, Cr: creatinine, GCs: glucocorticoids, HAQ-DI: health assessment questionnaire-disability index, IQR: interquartile range, LDA: low disease activity, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, S.D: standard deviation, SDAI: simplified disease activity index.

Different Impacts Of Gcs In The Three Age Groups

To investigate associations between GC use and impaired physical function in middle-aged, old, and very old patients, 3708 patients in both stage I/II and SDAI ≤11 were analyzed. We extracted statistically significant items in univariable analysis and selected clinically-important factors as covariates (age, sex, SDAI, GCs use, NSAIDs use, MTX use, bDMARD use, and newly-developing comorbidities requiring hospitalization) in multivariable logistic regression models. Association of GCs and age with impaired physical function were presented as adjusted OR for the 5 groups relative to

middle-aged patients without GCs as the reference group. Age was associated with impaired physical function, and the use of GCs further increased the adjusted OR from 1.49 (95%CI 1.23-1.81) to 2.57 (95%CI 2.06-3.20) in the old patients, and from 2.70 (95%CI 2.19-3.33) to 5.02 (95%CI 3.97-6.35) in the very old patients. Increased ORs in GC use compared to GC non-use were observed in all age groups, and the extent of the increase was comparable. Of note, as the age of the group increased, GCs use had a greater impact on impaired physical function (Table 4).

Table 4
Multivariable logistic regression models to examine associations of glucocorticoids and aging with impaired physical function.

	Patients in SDAI ≤11		Patients in SDAI ≤3.3	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
55-64 years/without GCs (reference)	1.00	-	1.00	-
55-64 years/with GCs[1]	1.70 (1.29-2.24)	<0.001	0.73 (0.21-2.56)	0.620
65-74 years/without GCs[1]	1.49 (1.23-1.81)	<0.001	2.03 (1.17-3.49)	0.011
65-74 years/with GCs[1]	2.57 (2.06-3.20)	<0.001	2.22 (1.13-4.36)	0.020
75-84 years/without GCs[1]	2.70 (2.19-3.33)	<0.001	4.01 (2.30-6.99)	<0.001
75-84 years/with GCs[1]	5.02 (3.97-6.35)	<0.001	6.81 (3.65-12.7)	<0.001
Gender, female	2.66 (2.26-3.14)	<0.001	1.73 (1.19-2.53)	0.004
NSAIDs	1.39 (1.23-1.58)	<0.001	1.40 (0.98-1.98)	0.061
MTX	0.69 (0.61-0.78)	<0.001	0.56 (0.41-0.78)	0.001
SDAI, per 1.0 increment	1.30 (1.27-1.33)	<0.001	1.72 (1.45-2.05)	<0.001
bDMARDs	1.93 (1.68-2.21)	<0.001	1.30 (0.88-1.91)	0.187
All hospitalization	2.03 (1.66-2.47)	<0.001	1.11 (0.61-2.00)	0.735

[1]Odds ratio of HAQ >0.5 for the 5 groups relative to middle-aged patients without GCs as the reference. Covariates: gender, SDAI, NSAIDs, MTX, bDMARDs, all hospitalization.

bDMARDs: biological disease-modifying anti-rheumatic drugs, CI: confidence interval, GCs: glucocorticoids, MTX: methotrexate, NSAIDs: non-steroidal anti-inflammatory drugs, SDAI: simplified disease activity index.

To minimize the influence of disease activity for physical function, we selected the 2078 patients in both stage I/II and SDAI ≤3.3 (SDAI remission). Multivariable analysis revealed an age-dependent increasing adjusted ORs of patients without GCs relative to middle-aged patients without GCs. Interestingly, the use of GCs further increased the adjusted OR from 4.01 (95%CI 2.30-6.99) to 6.81 (95%CI 3.65-12.7) in the very old patients, while the adjusted OR was 2.03 (95%CI 1.17-1.13) in the old patients without GCs, 2.22 (95%CI 1.13-4.36) in the old patients with GCs, and 0.73 (95%CI 0.21-2.56) in the middle-aged patients with GCs. Thus, in the patients in both remission and stage I/II, increased OR of GC use to GC non-use was observed only in the very old patients (Table 4).

Discussion

We confirmed that 31.4% or 27.4 % of the 11,036 patients aged 55-84 years in the Japanese national registry had achieved SDAI LDA or remission, respectively. The present study indicated that SDAI remission was associated with normal physical function (HAQ-DI ≤0.5) for both old and very old patients with disease in Steinbrocker stage I/II and is thus an appropriate goal not only for younger patients. Notably, we clarified that the negative impact of GCs on physical function increased with age in patients achieving SDAI LDA or remission. Interestingly, increased OR for impaired physical function in patients with GCs compared to those without GCs was observed in all age groups in SDAI LDA or remission, but in the patients in SDAI remission, it was observed only in the very old group, but not in the middle-aged group and old group. Our data indicated influence of GCs use for HAQ-DI >0.5 were different between the very old group and the old / middle-aged groups.

The present study showed that the proportion of MTX use in patients achieving LDA at stage I/II decreased with aging from middle-aged to old and then to very old, while GCs use increased with age. Previous cohort studies more than 10 years ago showed that GCs were more frequently given to older RA patients who received bDMARDs less often (14, 15). In the present analysis, we saw similar use of bDMARDs in all three patient age groups. This tendency is similar to that also seen in a nationwide survey using the Japanese insurance database (26), and is also seen for treatment of elderly-onset early RA (27). The present study also showed MTX was used less frequently in older patients receiving bDMARDs, and this was the same as the previous study (28–30).

In addition to disease activity, aging, joint damage and comorbidities influence physical function of RA patients who achieved clinical remission or LDA (31–35). Therefore, physical function might not normalize in the very old patients even when disease activity declined. To the disadvantage of older patients, comorbidities are associated with poorer treatment response or difficult-to-treat RA (12, 36). Since the strict goal-oriented therapy would be sometimes harmful in the elderly population as shown in the diabetes mellitus (37, 38), these suggested LDA might be a realistic goal of older RA in clinical practice to reduce the risk of DMARDs-related AEs. However, the present study showed that SDAI remission was associated with improvement of physical outcome in both very old and old patients.

The improvement of tender joint count, but not swollen joint count, was associated with the lower HAQ-DI in the old and very old patients. Previous reports for younger patients also showed tender joints were an important outcome from the point of view of the patients, while physicians attached greater importance to swollen joints (39).

Imaging and pathological studies showed more remarkable synovitis of elderly-onset RA compared to younger-onset RA (40, 41). Progressive joint destruction of elderly-onset rheumatoid arthritis was equal or higher compared with younger-onset RA (27, 42, 43). Initial failure of DMARDs was common in older patients with poor prognostic factors (27, 44), and adhere to T2T strategy targeting LDA improved functional outcome (45). However, it was difficult to stop GCs during 3 years in about 15 % of elderly-onset patients, and those patients had higher disease activity throughout 3 years (45). The present study also showed that very old / old patients given GCs in SDAI LDA had higher SDAI, lower proportion of MTX use, and more newly-developing comorbidities, than those not given GCs in SDAI LDA.

In the very old patients in SDAI remission, HAQ-DI was higher in patients with GCs than those without GCs, despite comparable disease activity in both groups. In contrast, in middle-aged patients in SDAI remission, HAQ-DI was similar between patients with or without GCs, despite higher disease activity in patients with GCs than in those without GCs. In the old patients, residual disease activity was likely to be related to physical function (Table3). Our multivariable analysis showed that, in the very old patients in SDAI remission, the adjusted OR of the very old patients with GCs increased compared to those without GCs. In the middle-aged and old patients, the adjusted OR of the patients with GCs did not increase compared to those without GCs (Table 4). These novel findings clearly demonstrated the impact of GC use on physical function differed between middle-aged, old, and very old patients. Factors other than disease activity might be involved in physical function of very old group. Tolerance to long-standing use of GCs might be lower in the

very old patients (17−19), and GC-associated comorbidities might be one of the associated factors with physical function in very old patients, but not in middle-aged and old patients.

A strength of this study is the use of data from a nationwide multicenter cohort representing approximately 2% of Japan's 850,000 RA patients (26). There are also several limitations to this study, including the following. First, the cross-sectional nature of the data makes it difficult to determine sustained SDAI LDA or remission. Second, it was difficult to determine whether the use of GCs caused the decline in physical functioning or was a result of declines in physical function. A third limitation is that the effectiveness of MTX or bDMARDs could not be longitudinally assessed. Forth, we collected data about complications requiring hospitalization and malignancy, but chronic diseases persisting for more than one year or GC-associated comorbidities could not be assessed.

Conclusions

Lower SDAI is a universal ideal goal for younger patients, and importantly, the present study showed that this was applicable for old and very old patients to enable them to achieve normal physical function. Notably, the negative impact of GCs was likely to most strongly influence physical function of very old patients than middle-aged or old patients, while the proportion of patients using GCs in those achieving LDA or remission increased with age. Protocols for tailoring therapy based on the patient's age should be developed when applying T2T strategies.

Abbreviations

ACPA: anti-citrullinated protein antibody, bDMARDs: biological disease-modifying anti-rheumatic drugs, BMI: body mass index, BUC: bucillamine,

C.I.: confidence interval, Cr: creatinine, CRP: C-reactive protein, csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs, EQ-5D: EuroQol 5 dimension, GCs: glucocorticoids, HAQ-DI: health assessment questionnaire-disability index, IGR: iguratimod, IQR: interquartile range, LDA: low disease activity, MTX: methotrexate, NinJa: National Database of Rheumatic Diseases in Japan, NSAIDs: non-steroidal anti-inflammatory drugs, OR: odds ratio, RA: rheumatoid arthritis, SASP: salazosulfapyridine, S.D: standard deviation, SDAI: simplified disease activity index, T2T: treat-to-target, TAC: tacrolimus, TNFi: TNF inhibitor, tsDMARDs: targeted synthetic DMARDs, VAS: visual analogue scale.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research in Japan. The study was approved by the Ethics Committee of Tokyo Medical and Dental University (M2016-232).

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

Authors' contributions

YK, TS, TI, and TM contributed to the study conception and design, methodology, and formal analysis. MM, ST and TM contributed to obtain funding. TS, MM, ST, SY and TM contributed to project administration. YK and TS drafted the original version of the manuscript, with the critical input of TI, SY, and TM. YK, FH, TM., MK, HS, TH, NK and TM contributed to date curation. All authors critically revised the report, commented on drafts of the manuscript, and approved the final report.

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