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Global assessments of disease activity are age-dependent determinant factors of clinical remission in rheumatoid arthritis

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ABSTRACT

Objective: The aim of the study is to assess the factors associated with clinical remission of patients with rheumatoid arthritis (RA) in daily clinical practice.
Methods: This analysis was based on the data of 304 RA patients in our center between May 2014 and March 2015. The following information was included: tender, swollen, and symptomatic joint counts, patient's and physician's global assessments, functional disability, laboratory and radiographic data, and RA treatments received.
Results: The patients were predominantly female (77.6%), with a median age of 71 years and a median disease duration of 5.8 years. Clinical remission rate, determined using the simplified disease activity index (SDAI), was 49.7%. Patient's and physician's global assessments (/10 cm) showed a higher score among patients who did not achieve SDAI remission than among those who did (median: 3.2 versus 0.3, $p < 0.0001$; and median: 1.8 versus 0.3, $p < 0.0001$, respectively). The contribution of serum C-reactive protein values (mg/dL) to SDAI was limited (median: 0.19 versus 0.06; $p < 0.0001$), as well as tender or swollen joint counts (median = 0 or 1). On multivariate analysis of factors not directly related to the disease activity, age was an independent risk factor for non-remission, and global assessment scores by patients and physicians showed an age-dependent increase, while counts of tender, swollen and symptomatic joints were comparable among elderly and non-elderly patients.
Conclusion: Global assessment of disease activity was age-dependent and independent of joint counts, and it provides a critical determinant of clinical non-remission.

Introduction

Recently, clinical remission has been accepted as the primary treatment goal for patients with rheumatoid arthritis (RA) [1]. An estimated 25–50% of patients with RA achieve clinical remission, as defined by the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria using the Boolean-based definition, simplified disease activity score (SDAI) [2–5]. This is also the rate of clinical remission achieved in clinical trials of patients with early RA initially treated with the combination of methotrexate (MTX) and biological disease-modifying antirheumatic drugs (bDMARDs) [6,7]. Understanding the barriers to achieving clinical remission, which stands at >50% of patients with RA, is necessary.

A recent study by Tymms et al. [8] identified a range of barriers to achieving clinical remission, including irreversible joint damage, patient-driven preferences, non-inflammatory musculoskeletal pain, insufficient time to assess the effect of recently initiated DMARDs, safety concerns, comorbidities, and a resistant disease status. Using a dataset from a United Kingdom randomized controlled trial with early RA patients, Ma et al. [9] identified age, sex, and tender joint count (TJC) as predictors of clinical remission.

The ACR/EULAR remission criteria, whether using the Boolean-based or composite measure SDAI score, include the following components: TJC, swollen joint count (SJC), patient's global assessment of disease activity (PtGA), serum C-reactive protein (CRP) level (mg/L), and, in addition, physician's global assessment of disease activity (MDGA) for SDAI [2].

Patients' perspective on remission in RA is largely defined by an absence or reduction of symptoms, a decreased impact of the disease on daily activities and a feeling of having returned to a normal life style [10]. Although patients' perspective is an essential component of the

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clinical assessment of RA, inclusion of the PtGA in the criteria for remission has been criticized as not being sufficiently accurate to provide an assessment of RA disease activity and often being the limiting factor for achieving clinical remission [11].

To further elucidate these issues, we conducted a cross-sectional analysis of a comprehensive dataset with the aim of identifying factors associated with clinical remission among patients with RA. The following self-reported outcomes were included in our analysis: self-assessment of at least 40 joints [28 joints evaluated in Disease Activity Score with 28-joint counts (DAS28) plus ankles and metatarsophalangeal joints] for the presence or absence of pain or considerable stiffness limiting activities of daily living [12], the PtGA, the Pain VAS, and the Health Assessment Questionnaire disability index (HAQ-DI). Our results indicate that elderly patients report higher global assessment of disease activity scores than younger patients, despite comparable patient- and physician-assessed joint counts between the age groups and normal values of inflammatory biomarker in most patients.

Patients and methods

The data of 304 patients with RA, followed at our center between May 2014 and March 2015, were included in our retrospective, cross-sectional analysis. All patients met the ACR 1987 revised criteria [13] and/or the ACR/EULAR 2010 classification criteria [14] for RA. In our daily practice, all patients complete the self-assessment of each joint for pain or considerable stiffness limiting their activities of daily living, with 40 joints (the 28 joints evaluated in the DAS28 plus the ankle and metatarsophalangeal joints). In addition, they also provide PtGA, Pain VAS, HAQ-DI before seeing a physician who evaluates TJC and SJC from $\geq$28 joints and MDGA on each visit. The following information was extracted from medical records for analysis: age, sex, disease duration from the time of RA diagnosis, TJC (28 joints) and SJC (28 joints), PtGA, Pain VAS and MDGA scored, all measured using a 100-mm VAS [15], the HAQ-DI, various biochemical markers, including erythrocyte sedimentation rate (ESR), serum CRP level, the presence of the rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) antibodies, and the RA treatment received. This study was approved by our institutional ethical committee (approval no. H16051), and the need for written informed consent was waived for this retrospective, observational study.

Statistical analysis

Statistical analysis was performed using JMP Pro (version 11.2, SAS Institute Japan Ltd. Tokyo, Japan). Continuous variables were summarized by the median and interquartile range (IQR), and analyzed by using the Mann–Whitney *U* test or the Kruskal-Wallis test. Binominal data between 2 groups were evaluated using Fisher's exact test or chi square test. The comparison of 2 groups with a control group was done by multiple comparisons of Dunnett's methods for continuous variables. The Cochran-Armitage test for trend was used for the comparison of categorical data among 3 age groups. A multivariate logistic regression analysis was performed to examine the conditional effects of clinical parameters on the achievement of SDAI remission. $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Of the 304 patients enrolled in our study, 77.6% were female. The median age of the study group was 71 years, with median disease duration of 5.8 years (Table 1). RF was positive in 67.8% ($n = 295$), with positive anti-CCP antibody identified in 71.1% ($n = 284$) of patients. The median for both TJC of 28 joints and SJC of 28 joints was '0,' with median values for the self-assessed painful and stiff joint counts (JC) of '1' and '0,' respectively. Median values for other measured factors were as follows: PtGA = 11 mm, Pain VAS = 11 mm, MDGA = 10 mm, HAQ-DI = 0.19, ESR = 20 mm/1 h, and CRP = 0.09 mg/dL. The distribution of DAS28-ESR and SDAI categories [16] was as follows: high = 4.3% and 3.3%, respectively; moderate = 21.4% and 12.5%, respectively; low = 21.1% and 34.5%, respectively; and remission = 53.3% and 49.7%, respectively. With regard to RA treatment, 63.5% of patients had received methotrexate (MTX) at a median dose of 8 mg/wk, 17.4% had received glucocorticoids at a median dose of 3 mg/d of prednisolone equivalent, and 29.6% had received bDMARDs.

Comparison of outcomes between patients who achieved SDAI remission and those who did not

Demographic and clinical features were compared between patients who achieved SDAI remission (49.7%) and those who did

Table 1
Patient characteristics ($n = 304$)

Sex (female), *n* (%)	236 (77.6)
Age (years), median (IQR)	71 (59–79)
Disease duration (years), median (IQR)	5.8 (2.6–10.9)
RF positive ($\geq$15 U/mL, $n = 295$), *n* (%)	200 (67.8)
Anti-CCP positive ($\geq$4.5 U/mL, $n = 284$), *n* (%)	202 (71.1)
TJC (/28 joints), median (IQR)	0 (0–1)
SJC (/28 joints), median (IQR)	0 (0–1)
Painful JC (/40 joints), median (IQR)	1 (0–3)
Stiff JC (/40 joints), median (IQR)	0 (0–2)
Pain VAS (/100 mm), median (IQR)	11 (2–31)
PtGA (/100 mm), median (IQR)	11 (2–32)
MDGA (/100 mm), median (IQR)	10 (3–19)
HAQ-DI, median (IQR)	0.19 (0–1)
Steinbrocker's radiographic stage (I/II/III/IV, $n = 289$), *n* (%)	147/39/38/65 (50.9/13.5/13.1/22.5)
ESR (mm/1 h), median (IQR)	20 (11–39)
CRP (mg/dL), median (IQR)	0.09 (0.03–0.30)
MTX, *n* (%)	193 (63.5)
MTX dose (mg/wk),* median (IQR)	8 (6–12)
Glucocorticoids, *n* (%)	53 (17.4)
Prednisolone equivalent dose (mg/d),* median (IQR)	3 (2–5)
bDMARDs, *n* (%)	90 (29.6)

Values are reported as the median (IQR) or number (%).

* Patients receiving MTX or glucocorticoids only.

Table 2
Comparison between remission and non-remission group based on the SDAI

Variables	SDAI remission (n = 151)	Non-remission (n = 153)	p Value
Sex (female), n (%)	111 (73.5)	125 (81.7)	0.099
Age (years), median (IQR)	70 (55–76)	73 (63–82)	0.0023
Elderly (age ≥ 65 years), n (%)	90 (59.6)	110 (71.9)	0.029
Disease duration (years), median (IQR)	5.6 (2.5–10.0)	5.9 (2.7–12.0)	0.60
Steinbrocker's radiographic stage (I/II/III/IV), n (%)	86/22/11/24 (60.1/15.4/7.7/16.8)	61/17/27/41 (41.8/11.6/18.5/28.1)	0.0011
RF positive, n (%)	89 (61.0)	111 (74.5)	0.018
RF titer (U/mL), median (IQR)	23.8 (5.1–101.8)	44.1 (14.0–113.5)	0.022
Anti-CCP positive, n (%)	95 (68.4)	107 (73.8)	0.36
Anti-CCP titer (U/mL), median (IQR)	37.4 (0.7–116)	42.4 (3.7–139.5)	0.37
Current MTX, n (%)	94 (62.3)	99 (64.7)	0.72
MTX dose (mg/wk),* median (IQR)	8 (6–12)	8 (6–12)	0.74
Current bDMARDs, n (%)	36 (23.8)	54 (35.3)	0.033
Current glucocorticoids, n (%)	22 (14.6)	31 (20.3)	0.23
Prednisolone equivalent dose (mg/d),* median (IQR)	2 (2–4.3)	3 (2–5)	0.11
TJC (/28 joints), median (IQR)	0 (0–0)	0 (0–3)	< 0.0001
SJC (/28 joints), median (IQR)	0 (0–0)	1 (0–3)	< 0.0001
Painful JC (/40 joints), median (IQR)	0 (0–1)	2 (0–5)	< 0.0001
Stiff JC (/40 joints), median (IQR)	0 (0–0)	0 (0–3)	< 0.0001
Pain VAS (/100 mm), median (IQR)	2 (0–8)	30 (15–52)	< 0.0001
PtGA (/100 mm), median (IQR)	3 (0–9)	32 (17–50)	< 0.0001
MDGA (/100 mm), median (IQR)	3 (0–8)	18 (11–26)	< 0.0001
HAQ-DI, median (IQR)	0 (0–0.3)	0.6 (0.1–1.6)	< 0.0001
CRP (mg/dL), median (IQR)	0.06 (0.03–0.15)	0.19 (0.04–0.68)	< 0.0001
ESR (mm/1 h), median (IQR)	16 (10–27)	26 (14–45)	< 0.0001

Values are reported as the median (IQR) or number (%).

* Patients receiving MTX or glucocorticoids only.

not (Table 2). Patients achieving SDAI remission were younger than those who did not (median: 70 versus 73 years; $p = 0.0023$), had less radiological evidence of joint damage ($p = 0.0011$; % stage III/IV, 24.5% versus 46.6%, $p = 0.0001$), lower frequency of positive RF (61.0% versus 74.5%; $p = 0.018$), and a lower proportion of patient treated using bDMARDs (23.8% versus 35.3%; $p = 0.033$). As expected, all activity-related parameters, such as joint counts, global assessments, and CRP, were significantly better among patients achieving SDAI remission than among patients who did not achieve remission.

Multivariate analysis of the factors associated with SDAI non-remission

To identify the factors associated with non-achievement of SDAI remission, we included the following variables in our multivariate analysis: sex, age, radiographic stage, RF titer, methotrexate dose, bDMARDs use, and prednisolone dose. In this model, age, radiographic stage, and bDMARDs use were identified as factors associated with SDAI remission (Table 3). Among these 3 variables, the association of irreversible joint damage and the use of bDMARDs, which was reserved for patients refractory to conventional synthetic DMARDs, with non-remission was reasonably understood.

Table 3
Multivariate analysis of the factors associated with SDAI non-remission

	Odds ratio	95% CI
Sex (female vs male)	1.8	0.95–3.4
Age (years)	7.3	2.1–28
Radiographic stage (III/IV versus I/II)	2.8	1.5–5.6
RF titer (U/mL)	0.30	0.0052–8.1
MTX dose (mg/wk)	1.9	0.78–4.7
bDMARDs (user versus non-user)	2.3	1.3–4.1
Prednisolone dose (mg/d)	2.6	0.54–13

Evaluation of age-specific effects on clinical remission

To elucidate the association of age with various clinical parameters, patients were stratified into the following 3 predefined age groups (Table 4): early-elderly (65 years ≤ age < 75 years), late-elderly (age ≥ 75 years) and non-elderly (age < 65 years). The following between-group differences were identified: The proportion of patients with anti-CCP decreased from the non-elderly (82.3%) to the early-elderly (67.1%) and late-elderly (64.2%) groups ($p = 0.0049$ by the Cochran-Armitage test for trend). As expected, due to safety concerns, the frequency of use of MTX and its dose were the lowest among patients in the late-elderly group (50.9% and 8 mg/wk), and was highest for the non-elderly groups (72.1%, 10 mg/wk; $p = 0.0010$ by the Cochran-Armitage test for trend). Subjective and objective joint counts were comparable among the 3 groups, while global assessment scores (pain VAS, PtGA, and MDGA), HAQ-DI, CRP, and ESR were the highest in the late-elderly group and the lowest in the non-elderly group. As a result, the SDAI score was the highest in the late-elderly group (median = 5.7) and lower in the early-elderly (median = 3.1) and non-elderly (median = 2.5) groups, and accordingly, the prevalence rate of SDAI remission was the lowest in the late-elderly group (39.5%) and higher in the early-elderly (52.3%) and non-elderly (58.7%) groups ($p = 0.0045$ by the Cochran-Armitage test for trend). This between-age difference in SDAI remission rate was principally attributable to the difference in the global assessment scores (PtGA and MDGA), with considering very low serum CRP levels among the majority of the patients. Of note, the SDAI remission rate was comparable among patients treated *with* and *without* MTX, regardless of the following age group: late-elderly group: 43.1% versus 35.7%, respectively, $p = 0.45$; early-elderly group: 46.7% versus 65.4%, respectively, $p = 0.16$ (both late- and early-elderly groups: 44.9% versus 45.1%, respectively, $p > 0.99$); and non-elderly group: 54.7% versus 69.0%, respectively, $p = 0.27$. Therefore, the lower remission rate in elderly patients cannot be directly attributable to a lower frequency and dose of MTX.

Table 4
Comparison between elderly (early- and late-elderly) and non-elderly patients

Variables	Late-elderly (n = 114)	Early-elderly (n = 86)	Non-elderly (n = 104)	p Value
Sex (female), n (%)	92 (80.7)	57 (66.3)	87 (83.7)	0.082
Disease duration (years), median (IQR)	5.4 (2.0–10.9)	7.1 (3.2–15.5)	5.4 (3.0–8.3)	0.57
Steinbrocker's radiographic stage (I/II/III/IV), n (%)	56/15/12/25 (51.9/13.9/11.1/23.2)	39/11/9/23 (47.6/13.4/11.0/28.1)	52/13/17/17 (52.5/13.1/17.2/17.2)	0.28
RF positive, n (%)	70 (63.1)	57 (67.9)	73 (73.0)	0.19
RF titer (U/mL), median (IQR)	32.0 (6.0–109.7)	37.8 (8.5–123.3)	27.2 (10.4–95.7)	0.65
Anti-CCP positive, n (%)	70 (64.2)	53 (67.1)	79 (82.3)	0.0035
Anti-CCP titer (U/mL), median (IQR)	98.2 (0.6–195.5)	30.7 (1.0–103.0)	33.5 (10.4–100.0)	0.75
Current MTX, n (%)	58 (50.9)	60 (69.8)	75 (72.1)	0.025
MTX dose (mg/wk),* median (IQR)	8 (6–10)	8 (6–12)	10 (8–12)	< 0.0001
Current bDMARDs, n (%)	36 (31.6)	27 (31.4)	27 (26.0)	0.36
Current glucocorticoids, n (%)	23 (20.2)	15 (17.4)	15 (14.4)	0.34
Prednisolone equivalent dose (mg/d),* median (IQR)	2 (2–5)	3 (2–4)	5 (2–5)	0.35
TJC (/28 joints), median (IQR)	0 (0–1)	0 (0–0)	0 (0–1)	0.80
SJC (/28 joints), median (IQR)	0 (0–2)	0 (0–2)	0 (0–1)	0.68
Painful JC (/40 joints), median (IQR)	1 (0–4)	0 (0–2)	1 (0–2)	0.40
Stiff JC (/40 joints), median (IQR)	0 (0–2)	0 (0–2)	0 (0–2)	0.40
Pain VAS (/100 mm), median (IQR)	17 (5–50)**	11 (3–25)	7 (0–22)	0.0019
PtGA (/100 mm), median (IQR)	20 (5–50)**	11 (3–28)	8 (1–25)	0.017
MDGA (/100 mm), median (IQR)	13 (5–21)**	10 (3–19)	6 (0–15)	0.0033
HAQ-DI, median (IQR)	0.6 (0–1.7)**	0.1 (0–0.5)	0 (0–0.5)	< 0.0001
CRP (mg/dL), median (IQR)	0.18 (0.05–0.45)**	0.06 (0.04–0.27)	0.06 (0.02–0.15)	0.0007
ESR (mm/1 h), median (IQR)	30 (17–46)**	22 (12–40)**	14 (7–23)	< 0.0001
SDAI, median (IQR)	5.7 (1.7–11.0)**	3.1 (0.8–7.5)	2.5 (1.0–6.9)	0.018
SDAI remission, n (%)	45 (39.5)	45 (52.3)	61 (58.7)	0.029

Values are reported as the median (IQR) or number (%), with p values for elderly (early-elderly and late-elderly; n = 200) reported relative to the non-elderly group.

* Patients receiving methotrexate or glucocorticoids only.

** $p < 0.05$ by multiple comparisons with non-elderly patients (Dunnett's methods).

Discussion

In our clinical practice, SDAI remission is generally achieved in 50% of patients with RA. This retrospective analysis identified older age as an independent risk factor for non-remission. Our results further identified that elderly patients expressed higher global assessments of pain and stiffness affecting their daily life, although their self-assessed joint counts and objective joint counts were comparable to counts reported by non-elderly patients. Moreover, the majority of patients among all age groups had normal levels of inflammatory biomarkers.

SDAI is the sum of TJC28, SJC28, PtGA (/10 cm), MDGA (/10 cm), and CRP (mg/dL). Noting an IQR of CRP (mg/dL) of 0.04–0.68, even in elderly patients, the difference in SDAI between elderly and non-elderly patients was found to be chiefly attributable to differences in PtGA (/10 cm) score (elderly: median = 1.5 (range: 0.3–3.7); non-elderly: median = 0.8; range: 0.1–2.5; $p = 0.017$) and MDGA (/10 cm) score (elderly: median = 1.2 (range: 0.4–2.0); non-elderly: median = 0.6 (range: 0–1.5); $p = 0.0033$). These between-group differences in global assessment scores have a direct effect on the Boolean-based remission rate: 39.0% among elderly patients (36.0% in late-elderly and 43.0% in early-elderly patients) compared to 51.9% among non-elderly patients ($p = 0.038$). For this reason, we used the SDAI to define clinical remission in this study.

The higher PtGA and Pain VAS reported by elderly patients, compared to non-elderly patients, despite comparable joint counts, might be explained by between-group differences in the distribution of affected joints, the severity and/or sensitivity of pain at each joint, as well as by differences in non-RA factors such as health comorbidities including osteoarthritis and spinal spondylosis. It is also important to note the difficulty in meeting RA remission criteria in a general population of elderly individuals without RA [17], as well as by patients with RA with comorbidities, such as degenerative spine disease [18–20]. The effect of age on RA outcome was identified even in a cohort of patients with early RA, the ESPOIR cohort [21]. Thus, although patient-reported outcome (PRO) is undoubtedly important in the care of rheumatic diseases, including RA, the method for incorporating PROs in the determination of disease activity and clinical outcomes should be reconsidered.

Systemic inflammation, indicated by elevated ESR and serum CRP level, was more evident among elderly than among non-elderly patients, as previously reported [22]. Elevated ESR and serum CRP level, which could be indicative of less stringent management of RA among elderly than among non-elderly patients, may reflect higher load of comorbidities among elderly patients. Although the frequency and dose of MTX were significantly lower in our study cohort among elderly than among non-elderly patients, the dose was actually comparable when age-related renal function was considered. Moreover, the use of MTX was comparable among elderly patients who achieved SDAI remission and those who did not (58.9% versus 59.1%, respectively; $p = 1.00$). Furthermore, the frequency of use of bDMARDs and glucocorticoids was higher among elderly than among non-elderly patients (Table 4). Therefore, the difference in remission rate between elderly and non-elderly patients could not be adequately explained by differences in RA treatment.

The limitations of our study need to be acknowledged, including a relatively small sample size from a single center and the lack of objective data to quantify disease severity by high-sensitivity imaging, such as ultrasound or magnetic resonance imaging. However, we did consider sufficient clinical information in our analysis, including self-assessed joint counts, HAQ-DI, and radiographic evaluations, which is a strength of our study.

Conclusions

Clinical remission was achieved in 50% of patients with RA in our daily clinical practice. In this study, we identified the global assessment of disease activity reported by patients and physicians as a critical factor in determining SDAI remission in elderly patients. An optimal evaluation and management strategy for RA

in elderly patients remains to be defined and would be of particular importance in Japan, where the mean population is older than anywhere in the world.

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