Rheumatoid arthritis patients with low baseline Health Assessment Questionnaire scores have a risk of functional disability progression: a *post hoc* analysis of a nationwide longitudinal cohort in Japan

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Abstract

Objective

To determine prognostic factors for the Health Assessment Questionnaire-Disability Index (HAQ-DI) progression in patients with rheumatoid arthritis (RA) in clinical practice.

Methods

We evaluated 388 biological disease-modifying anti-rheumatic drug (bDMARD)-naïve Japanese patients with RA with moderate to high disease activity at study entry after being treated with conventional synthetic DMARDs. These patients were treated according to a treat-to-target (T2T) strategy for one year. The Disease Activity Score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR) and the HAQ-DI were assessed every three months. We also evaluated joint destruction using a modified total Sharp score at baseline and at one year. HAQ-DI progression was defined as the yearly progression of HAQ-DI >0.1. We performed a multiple logistic regression analysis to explore the factors predicting HAQ-DI progression at one year.

Results

HAQ-DI progression was observed in 18% of the patients. The multiple logistic regression analysis revealed the independent variables associated with HAQ-DI progression were: DAS28-ESR >5.1 at baseline (odds ratio [OR] 0.31, 95% confidence interval [CI] 0.13–0.74, p=0.0083); HAQ-DI score at baseline <0.5 (OR 2.27, 95% CI 1.22–4.26, p=0.0102); and achievement of low disease activity at 12 weeks (OR 0.42, 95% CI 0.21–0.82, p=0.0112).

Conclusion

Our data suggest that maintaining clinical improvement according to T2T and initiating the treatment at an early stage are important for functional improvement after one year and that patients with low baseline HAQ scores have a higher risk of HAQ disability progression.

Key words

rheumatoid arthritis, HAQ-DI progression, treat-to-target

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterised by progressive joint destruction, leading to reduced quality of life and premature mortality (1, 2). The goal of RA treatment is to achieve clinical, structural, and functional remission (3). Among these remissions, functional remission is important because of an association between functional disability and increased cardiovascular and all-cause mortality (4) and work disability (5) in RA patients.

The Health Assessment Questionnaire (HAQ) is the most commonly survey of functional disability in both clinical trials and observational studies (6). Previous studies have identified many factors that predict HAQ disability progression. Functional disability predictors include baseline HAQ score (7), older age (8), female sex (8), disease activity (7, 8), rheumatoid factor positivity or anti-citrullinated protein antibody positivity (9), radiographic damage (10), the number of comorbidities (11), and low socioeconomic status (12). However, the prognostic factors of HAQ disability progression vary, and there have been no large-scale, multicentre, prospective studies that collected clinical findings with images.

We previously conducted a nationwide, multicentre, prospective study in Japan and reported prognostic factors for clinically relevant radiographic progression in RA patients whose clinical disease activity was moderate to high (13) and those with low disease activity (LDA) at enrolment (14). Using this observational cohort, we identified factors predicting HAQ disability progression after one year in RA patients with moderate to high disease activity.

Methods

Patients

We performed a *post hoc* analysis of a nationwide cohort study registered with the University Hospital Medical Information Network Clinical Trials Registry (http://www.umin.ac.jp/ctr/) (no. UMIN000014791), conducted in daily RA clinical practices in Japan. The inclusion criteria were as follows: 1. RA patients who met the American College of Rheumatology (ACR) 1987 criteria (15) or the 2010 RA classification criteria (1); 2. The patient's clinical disease activity determined by the Disease Activity Score 28 joints-erythrocyte sedimentation rate (DAS28-ESR) is moderate to high or, obvious plain radiographic erosion is confirmed at enrolment; 3. RA patients taking conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) but not biological DMARDs (bDMARDs) at enrolment. Overall, 887 bDMARDs-naïve patients with RA, from 26 centres affiliated with Nagasaki University or Tohoku University in Japan, were recruited as the study cohort between May 2009 and March 2012. All patients were examined and treated by Japan College of Rheumatology (JCR)-certified rheumatologists.

When a patient relapsed during the present study, one of the participating JCR-certified rheumatologists treated the patient using a T2T strategy that included using bDMARDs. We observed all the patients for one year after their respective enrolment and assessed their RA disease activity every three months using the DAS28-ESR and the Health Assessment Questionnaire-Disability Index (HAQ-DI) (16). According to a previous report suggesting that the minimal clinically important difference is 0.1 (17), we defined HAQ-DI progression as yearly HAQ-DI progression >0.1. In this *post hoc* analysis, we have defined a flare according to previously validated criteria: during the one-year, a DAS28-ESR increase of >1.2 or >0.6 if DAS28-ESR ≥3.2 (18).

All patients provided signed informed consent to be included in the protocol, which was approved by the Institutional Review Board of Nagasaki University (approval no.: 10022570-2), Tohoku University, and affiliated centres.

To evaluate the patients' structural damage, radiographs of each patient's hands and feet were obtained at baseline and at one year, and the images were evaluated by two independent rheumatologists blinded to clinical evaluation, using the van der Heijde-modified total Sharp score (mTSS) system as previously described (13, 19).

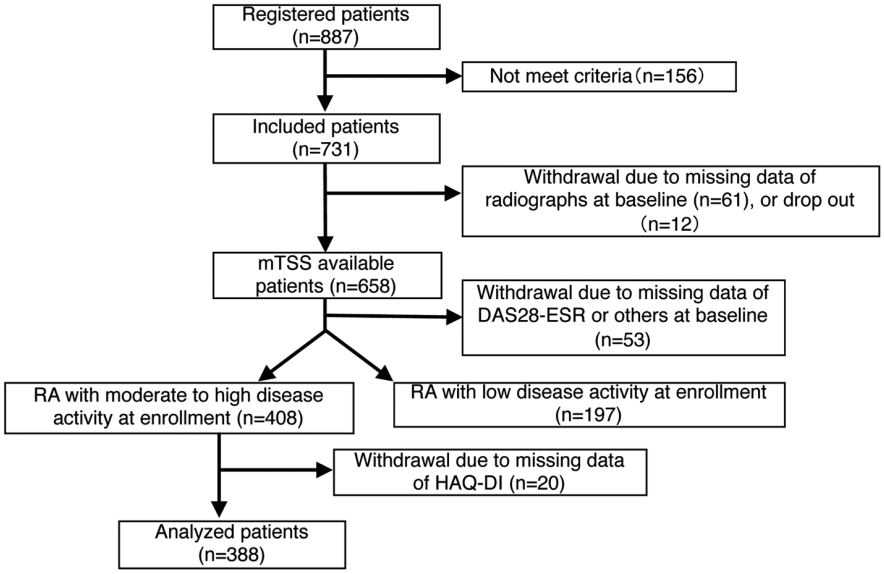

Fig. 1. Patient enrolment flow chart and the therapeutic course during the one-year observation after baseline in our RA cohort.
mTSS: modified total Sharp score; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index.

Table I. The baseline demographic, clinical, and radiographic characteristics of RA patients in this study.

Variables	All patients (n=388)
Demographic	
Age, years	61.0 (12.3*)
Female, n, %	301 (78)
Disease characteristics	
Disease duration, years	3.2 (1.0–7.9)
RF or ACPA positive, n, %	281 (80) n=352
Disease activity	
DAS28-ESR at baseline	4.27 (3.67–5.14)
CRP at baseline, mg/dL	0.42 (0.14–1.31) n=386
ESR at baseline, mm/hour	31 (18–48)
HAQ-DI at baseline	0.50 (0.125–1.00)
HAQ-DI < 0.5 at baseline, n, %	222 (57)
Radiographs	
mTSS at baseline	13.5 (4.5–49.25)
Erosion score at baseline	7.75 (2.1–28)
JSN score at baseline	5.5 (1–22)
Treatment	
Methotrexate use, n, %	281 (73) n=384
Dose of methotrexate at baseline, mg/week	7.3 (2.2*) n=281
Maximum dose of methotrexate during 1 year, mg/week	8.2 (2.4*) n=297
Prednisolone use, n, %	148 (38)
bDMARD introduction within 12 weeks, n, %	71 (18.2)
LDA at 12 weeks, n, %	122 (32) n= 81

*Mean values (SD), median (interquartile range) or number (percentages) are shown. RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; DAS28-ESR: Disease Activity Score 28 joints-erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Disability Index; mTSS: modified total Sharp score; JSN: joint space narrowing; bDMARD: biological disease-modifying antirheumatic drug; LDA: low disease activity.

Statistical analysis

The baseline demographic, clinical, and radiographic characteristics of the RA patients were summarised, with frequencies and percentages for the categorical data, mean plus standard deviation, and median plus interquartile range for continuous data. The differences between patients with and without HAQ-DI progression were assessed using Fisher's exact test for the categorical variables and Wilcoxon's rank sum test for the continuous variables. To determine the independent predictive factors for HAQ-DI progression at one year, we performed a multiple logistic regression analysis. We selected variables with p-values <0.05 by univariate analyses. All tests were two-sided, and a p-value <0.05 was considered statistically significant. The statistical analyses were performed using JMP Pro 13.0, GraphPad Prism 7.0 software, or SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

Patients

Figure 1 shows the patient enrolment flow chart. Since we performed a complete case analysis, cases with any missing data at baseline or cases with dropout were excluded from our study. As a result, patients with moderate to high disease activity, excluding cases with no HAQ-DI data, were included in the analysis. Clinical demographics between analysed (n=388) and excluded cases (n=20) were not significantly different (data not shown).

The patients' characteristics are shown in Table I. The patients' mean age was 61.0 years, and the median disease duration was 3.2 years. The median DAS28-ESR at baseline was 4.27, the median HAQ-DI at baseline was 0.5, and the median mTSS at baseline was 13.5. During the one-year observation period, 71 patients initiated bDMARD treatment within 12 weeks after the enrolment.

The clinical course during one year following baseline is shown in Figure 2. During the one-year observation, the median DAS28-ESR and HAQ-DI improved significantly, from 4.27 to 3.16 (p=0.0091 at baseline *vs*. one year, Fig. 2A) and from 0.5 to 0.25 (p<0.0001 at baseline *vs*. one year, Fig. 2B), respectively. We found the median mTSS score increased from 13.5 to 15 (p<0.0001 at baseline *vs*. one year, Fig. 2C). During the study, there were 126 (33%) patients who experienced a flare of the disease as defined above. Among the 126 patients, 46 patients were treated with increase/change csDMARDs, 18 patients were treated with a bDMARD, and 3 patients were

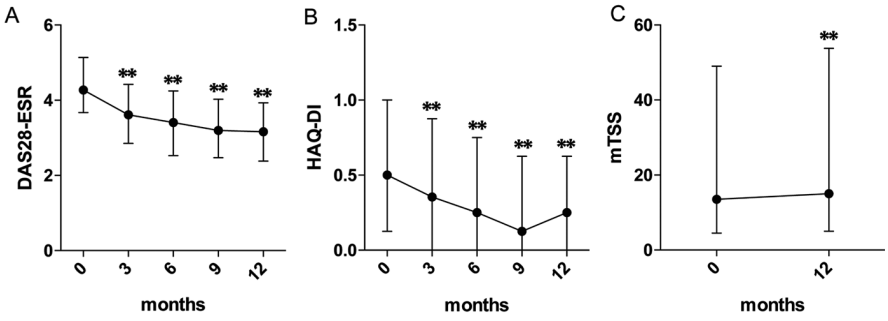

Fig. 2. The clinical course during one year following baseline.
DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; mTSS: modified total Sharp score.

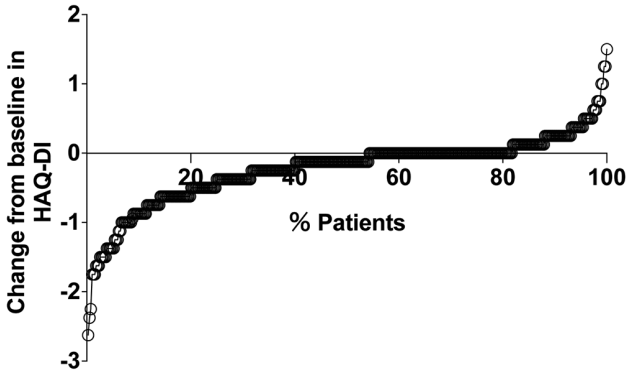

Fig. 3. Cumulative probability plots during one year post-baseline as assessed by HAQ-DI. HAQ-DI: Health Assessment Questionnaire-Disability Index.

treated with increase csDMARDs and introduction of bDMARDs. HAQ-DI progression
(ΔHAQ-DI >0.1) was observed in 71 (18%) of the 388 patients. Cumulative probability plots at one year post-baseline, as assessed by HAQ-DI, are shown in Figure 3.

Prediction of HAQ-DI progression at one year in the patients with RA

To determine which variables were associated with HAQ-DI progression at one year, we evaluated 22 variables, as shown in Table II. Five continuous variables (DAS28-ESR, HAQ-DI, mTSS, erosion [ERO] score, and joint space narrowing [JSN] score) were dichotomised considering clinical relevance and validity. We found the 10 variables significantly associated with HAQ-DI progression in the univariate analysis were female sex, DAS28-ESR at baseline, DAS28-ESR >5.1 at baseline, C-reactive protein at baseline, HAQ-DI at baseline, HAQ-DI <0.5 at baseline, mTSS at baseline, JSN score at baseline, JSN score >5.5 at baseline, and non-achievement of LDA at 12 weeks. To determine the prognostic factors for HAQ-DI progression, we subsequently performed a multiple logistic regression analysis with five independent nominal variables as follows: female sex, DAS28-ESR >5.1 at baseline, HAQ-DI <0.5 at baseline, JSN score >5.5 at baseline, and achievement of LDA at 12 weeks. We found three prognostic factors for HAQ-DI progression, as follows: DAS28-ESR >5.1 at baseline (odds ratio [OR] 0.31, 95% confidence interval [CI] 0.13–0.74, p=0.0083), HAQ-DI score at baseline <0.5 (OR 2.27, 95% CI 1.22–4.26, p=0.0102), and achievement of LDA at 12 weeks (OR 0.42, 95% CI 0.21–0.82, p=0.011). Female sex and JSN >5.5 at baseline were not significantly associated with HAQ-DI progression in a multiple regression analysis.

Discussion

HAQ disability progression indicates deteriorated physical function and is an important functional prognosis. In the present study, we identified that DAS28-ESR ≤5.1 at baseline, HAQ-DI < 0.5 at baseline, and non-achievement of LDA at 12 weeks are prognostic factors for HAQ-DI progression among patients with RA with moderate to high disease activity at study entry. We confirmed prognostic factors for HAQ-DI progression by a large-scale, multicentre, prospective study using longitudinal clinical manifestations and radiographic changes.

Our study showed that patients with a lower HAQ-DI and lower DAS28-ESR at baseline tended to present HAQ progression after one year. These observations were consistent with a previous report (11). This report mentioned that yearly HAQ disability progression rates were higher in patients with mild to inactive RA than in those with moderate to severe RA, and patients with HAQ disability progression were characterised by low HAQ scores at baseline. Accordingly, RA patients with higher disease activity already had functional impairment and a lower possibility of HAQ disability progression. Although patients with low baseline HAQ scores had higher HAQ remission rates with bDMARD treatment (20), On the other hand, they have a higher risk of HAQ disability progression. When we compare the treatment content between the HAQ-DI progression group and the group without HAQ-DI progression, there was no significant difference in the amount of methotrexate during the study period or in the early bDMARD introduction rate within 12 weeks.

Since maintaining disease activity without a flare has been suggested to prevent HAQ progression (21), we analysed the association between an experience of flare and HAQ-DI progression. We found a significant association between an experience of flare during the one year and HAQ-DI progression (OR 4.73, 95% CI 2.74–8.16, p<0.001). In addition, we also analysed whether baseline HAQ-DI predicts a flare of the disease during the follow-up period and found that baseline HAQ-DI <0.5 was significantly associated with a flare (OR 1.72, 95% CI 1.10–2.69, p=0.0203). These observations indicate that lower HAQ-DI at baseline predicts a flare that contributes to HAQ-DI progression.

Rapid achievement of remission in RA patients may prevent subsequent joint destruction (22), suggesting the impor-

Table II. Association between baseline characteristics and HAQ-DI progression at one year (univariate analyses).

Variables	ΔHAQ >0.1 (n=71)	ΔHAQ ≤0.1 (n=317)	*p*-value
Demographic			
Age, years	64 (53–70)	62 (54–71)	0.72
Female, n, %	63 (89)	238 (75)	0.012
Disease characteristics			
Disease duration, years	3.2 (1.62–7.00)	3.2 (0.82–8.04)	0.41
RF or ACPA positive, n, % (n=352)	51 (77)	230 (80)	0.61
Disease activity			
DAS28-ESR at baseline	4.10 (3.60–4,72)	4.36 (3.71–5.26)	0.0063
DAS28-ESR >5.1 at baseline, n, %	7 (10)	96 (30)	0.0003
CRP at baseline, mg/dL	0.3 (0.1–0.78)	0.5 (0.16–1.40)	0.027
ESR at baseline, mm/hour	27 (15–45)	31 (18.5–48.5)	0.28
HAQ-DI at baseline	0.25 (0–0.625)	0.5 (0.125–1.06)	0.0075
HAQ-DI <0.5 at baseline, n, %	52 (73)	170 (54)	0.0033
Radiographs			
mTSS at baseline	30 (6–67.5)	12.5 (4.25–43.75)	0.035
TSS >13.5 at baseline, n, %	41 (58)	152 (48)	0.15
Erosion score at baseline	14 (2.5–42.5)	7.5 (2–25.25)	0.083
Erosion score > 7.75 at baseline, n, %	42 (59)	152 (48)	0.11
JSN score at baseline	12 (1.5–33)	5 (1–20)	0.027
JSN score > 5.5 at baseline, n, %	45 (63)	147 (46)	0.012
Treatment			
Methotrexate use, n, %	51 (72)	244 (77)	0.36
Dose of methotrexate at baseline, mg/week (n=281)	6 (6–8)	8 (6–8)	0.054
Maximum dose of methotrexate during 1 year, mg/week (n=297)	8 (6–10)	8 (6–10)	0.84
Prednisolone use, n, %	29 (41)	119 (36)	0.69
bDMARD introduction within 12 weeks, n, %	9 (13)	62 (20)	0.23
LDA at 12 weeks, n, % (n=381)	14 (20)	108 (35)	0.016

p-values were established using Fisher's exact test or Wilcoxon's rank sum test. Median (interquartile range) or number (percentages) are shown. RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; DAS28-ESR: Disease Activity Score 28 joints-erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire-Disability Index; mTSS: modified total Sharp score; JSN: joint space narrowing; bDMARD: biological disease-modifying anti-rheumatic drug; LDA: low disease activity.

tance of rapid improvement of disease activity. Our cohort showed that the non-achievement of LDA at 12 weeks predicted HAQ disability progression at one year. Although no large cohort has investigated the relationship between treatment response and HAQ disability progression, our data suggest that a rapid achievement of LDA or remission, according to T2T, is important for preventing subsequent functional impairment.

A previous report indicated that the JSN score, rather than the ERO score, is associated with functional disability, suggesting cartilage damage is associated with HAQ disability progression rather than bony damage (23). In consistent with this report, our data in univariate analysis indicated that mTSS score and JSN score at baseline were associated with HAQ-DI progression, but the ERO score at baseline was not. However, a JSN >5.5 at baseline was not significantly different in the multiple logistic regression analysis.

There are some study limitations to acknowledge. First, the follow-up period was only one year. Given that functional disability in RA progresses over several years, long-term verification studies are needed to confirm our results. Accordingly, although some reports define HAQ disability progression as ΔHAQ-DI >0.22 (17), we defined ΔHAQ-DI >0.1 as HAQ disability progression. Second, we did not evaluate the individual HAQ-DI domain or items that contributed to HAQ disability progression. Similarly, it would be desirable to analyse the mTSS score of the feet and hand regions separately.

Conclusions

In conclusion, this is the first prospective observational study to examine predictive HAQ disability progression among Japanese RA patients who are treated with DMARDs in daily practice. Our findings indicate that rapid clinical improvement, according to T2T, is important for functional improvement after one year, and patients with low baseline HAQ scores have a higher risk of HAQ disability progression. Further research is needed on factors that predict long-term functional prognosis.

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