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LETTER

Non-synonymous variant (Gly307Ser) in *CD226* is associated with susceptibility in Japanese rheumatoid arthritis patients

Taku Suzuki · Katsunori Ikari · Yasushi Kawaguchi · Koichiro Yano · Takuji Iwamoto · Manabu Kawamoto · Yoshiaki Toyama · Atsuo Taniguchi · Hisashi Yamanaka · Shigeki Momohara

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Autoimmune diseases (ADs) are characterized by an abnormal immune response to self-antigens, and are believed to share a common pathogenesis. For example, the *PTPN22* risk allele (620Trp) dramatically increases susceptibility to rheumatoid arthritis (RA), type 1 diabetes (T1D), systemic lupus erythematosus (SLE) and autoimmune thyroid disease [1], and *STAT4* is also associated with RA, SLE, and systemic sclerosis (SSc) [2, 3]. A genome-wide association study in a Caucasian population also associated susceptibility to T1D with an SNP (rs763361; Gly307Ser) in the *CD226* gene [4]. The *CD226* glycoprotein, a 67 kDa a member of the immunoglobulin superfamily, is involved in regulating T-cell adhesion and activation [5]. The *CD226* Gly307Ser variant has also been associated with susceptibility to several ADs across different racial groups, including RA in Caucasian, Colombian, and Chinese populations [6–8].

T. Suzuki · K. Ikari (✉) · Y. Kawaguchi · K. Yano · T. Iwamoto · M. Kawamoto · A. Taniguchi · H. Yamanaka · S. Momohara
Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada, Shinjuku, Tokyo 162-0054, Japan
e-mail: kikari@ior.twmu.ac.jp

T. Suzuki · T. Iwamoto · Y. Toyama
Department of Orthopaedic Surgery, Keio University, Tokyo, Japan

Genetic risks may differ among different populations and sometimes even among groups in the Asian ethnicities [9, 10]. Therefore, replicating previously reported genetic associations in other populations is essential in order to establish the associations as well as to reveal the magnitude of the genetic risk in each population. We undertook a case–control study in a Japanese RA cohort to support the interethnic consistency of the association of the *CD226* variant with disease susceptibility in Japanese AD patients diagnosed with RA, SLE, and SSc.

The Tokyo Women's Medical University Genome Ethics Committee approved the study, and each participant signed an informed consent form following a verbal explanation of the study. The case–control study was performed using Japanese DNA donors: 1504 RA patients, 243 SLE patients, 189 SSc patients, and 752 ethnically matched population controls (Table 1). The American College of Rheumatology criteria for the diagnosis of RA, SLE, and SSc were used to identify patients for the study [11–13].

The SNP (rs763361) in *CD226* was selected based on evidence for an association in RA patients [4, 6]. TaqMan SNP genotyping was performed according to the manufacturer's instructions (Applied Biosystems, Tokyo, Japan). Duplicate samples and negative controls were included to monitor accuracy. The chi-square test was performed to compare allelic frequencies of the variant and to test for Hardy–Weinberg equilibrium (HWE). Stratified analysis using rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) status was performed to test whether the putative genetic risk factor is predominant in the autoantibody-positive subset of RA patients. These analyses were performed using the R software package (http://www.r-project.org/).

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The genotyping success rate was greater than 99% and the genotype concordance rate was 100% as assessed by duplicate samples. The genotypic distribution of the Gly307Ser variant was in HWE. There was no gender difference in the allelic distribution of the polymorphism in controls ($P = 0.94$). Allele frequencies are shown in Table 2. The 307Ser allele was significantly associated with RA in the Japanese population [$P = 0.01$, odds ratio (OR) = 1.17 (1.03–1.33)]. The allele showed a trend for association with SSc [$P = 0.08$, OR = 1.23 (0.97–1.55)], but no association was found with SLE [$P = 0.44$, OR = 1.08 (0.88–1.34)]. Stratification analysis revealed that 307Ser is a risk factor for RA in autoantibody-positive patients in the presence of RF [$P = 0.007$, OR = 1.19 (1.04–1.36)] and ACPA [$P = 0.009$, OR = 1.19 (1.05–1.36)].

Table 1 Demographics of AD patients

RA	
Age, years (median)	60
Sex, female (%)	84
RF positive (%)	88
ACPA positive (%)	87
SLE	
Age, years (median)	34
Sex, female (%)	94
SSc	
Age, years (median)	41
Sex, female (%)	90
Controls	
Age, years (median)	35
Sex, female (%)	50

RF rheumatoid factor, *ACPA* anti-cyclic citrullinated peptide antibody, *SSc* systemic sclerosis

Recent studies have indicated that the genetic background of RA might vary among ethnic groups. While the genetic association between HLA–DRB1 and RA susceptibility is well established in most populations, other reported associations with genes such as *PTPN22* and *PADI4* have been difficult to replicate in different populations [14, 15]. The results of this report support previous studies indicating that a variant on *CD226* is a genetic risk factor for RA across different racial groups. The overall OR for the variant on RA susceptibility was 1.2 in non-European populations; slightly higher than previously reported for Europeans (1.09) [6].

This was the first attempt to test the association between Gly307Ser, the putative disease causal variant for a variety of autoimmune diseases, and SSc in Japanese. Though we found a trend for an association with SSc that had an OR similar to that of RA, it was not significant. We also observed no association between the variant and SLE. One possible reason for the negative associations is the lack of statistical power. While the sample size of RA provided a statistical power of 0.94 with an OR = 1.25 [7] and a T allele frequency = 0.477 (Japanese HapMap Japanese Project), the sample sizes of SLE and SSc could not provide enough power (<0.8). Further large-scale study is needed to verify the association of 307Ser and SSc, since the population we used was relatively small ($n = 189$). Another possible reason for the negative associations is that the contribution of *CD226* to the disease pathway may differ between RA and SLE or SSc. Other independent association studies would help to improve the hypothesis.

Thus, replication studies using other ethnic populations are useful to establish genetic association and to define the genetic impact in each ethnic population. We conclude that we have successfully validated the association of *CD226* Gly307Ser with RA susceptibility in a Japanese population.

Table 2 Genotype distributions of Gly307Ser in AD patients and controls

Phenotype	Genotype			Total	MAF	OR (95% CI)	*P*
	CC	CT	TT				
RA	417	727	355	1479	0.47	1.17 (1.03–1.33)	0.01
RF positive	365	636	304	1305	0.48	1.19 (1.05–1.36)	0.007
RF negative	50	91	31	172	0.45	1.05 (0.82–1.34)	0.69
ACPA positive	355	602	294	1251	0.48	1.19 (1.04–1.36)	0.009
ACPA negative	45	107	31	183	0.46	1.12 (0.89–1.42)	0.32
SLE	76	114	53	243	0.45	1.08 (0.88–1.34)	0.44
SSc	48	94	42	184	0.48	1.23 (0.97–1.55)	0.08
Control	236	372	136	744	0.43		

Gly glycine, *Ser* serine, *RA* rheumatoid arthritis, *MAF* minor allele frequency, *OR* odds ratio, *CI* confidence interval, *RF* rheumatoid factor, *ACPA* anti-cyclic citrullinated peptide antibody, *SSc* systemic sclerosis

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Conflict of interest The authors declare that there is no conflict of interest.

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The Influence of Individual Joint Impairment on Functional Disability in Rheumatoid Arthritis Using a Large Observational Database of Japanese Patients

KUMI SHIDARA, EISUKE INOUE, DAISUKE HOSHI, EIICHI TANAKA, YOHEI SETO, AYAKO NAKAJIMA, SHIGEKI MOMOHARA, ATSUO TANIGUCHI, and HISASHI YAMANAKA

ABSTRACT. ***Objective.*** To clarify the influence of individual joint impairment on functional capacity through a retrospective study with a 3-year interval, using a large cohort of Japanese patients with rheumatoid arthritis (RA).

Methods. Subjects included 3457 patients with RA who participated in a large observational cohort study in both April 2004 and April 2007; 43 joints were assessed and classified into 10 joint areas. Impairment of each joint area was scored based on the presence of swelling or tenderness: score 0 (no swelling or tenderness in either joint), score 1 (swelling or tenderness in a unilateral joint), and score 2 (swelling or tenderness in bilateral joints). Score change was defined as the difference between scores from 2004 and 2007. The Japanese validated version of the Health Assessment Questionnaire is the J-HAQ; ΔJ-HAQ score was determined by subtracting J-HAQ score in 2007 from that in 2004. The relationship between score change and ΔJ-HAQ score, and the effect of joint impairment on ΔJ-HAQ score were assessed.

Results. Major joint areas that contributed to ΔJ-HAQ score included the wrist (31%), shoulder (21%), knee (13%), and ankle (10%). The shoulder, wrist, knee, and ankle in the worsening group were associated with a J-HAQ score increase of 0.13 to 0.18 compared to the improvement group.

Conclusion. Our study demonstrated that impairment of the shoulder, wrist, knee, and ankle significantly affects functional capacity in patients with RA. Care of these joints is suggested to be especially important for better functional outcomes. (First Release Jan 15 2012; J Rheumatol 2012;39:476–80; doi:10.3899/ jrheum.110770)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
JOINT INVOLVEMENT
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From the Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan.

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K. Shidara, MD; E. Inoue, PhD; D. Hoshi, MD; E. Tanaka, MD; Y. Seto, MD; A. Nakajima, MD; S. Momohara, MD; A. Taniguchi, MD; H. Yamanaka, MD, Institute of Rheumatology, Tokyo Women's Medical University.

Address correspondence to Dr. K. Shidara, Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo, Japan 162-0054. E-mail: kumi-shi@ior.twmu.ac.jp

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Rheumatoid arthritis (RA) is characterized by persistent polyarthritis and progressive joint damage that lead to functional disability. Suppression or improvement of functional disability is one of the major goals of RA treatment. Previous studies showed that Health Assessment Questionnaire (HAQ) score is associated with disease activity, joint distraction, disease duration, age, sex, muscle strength, work disability, and mortality[1,2,3,4,5,6]. RA disease activity has been shown to be significantly associated with decreased HAQ scores throughout the course of RA[1,2].

Functional disability in patients with RA has both reversible and irreversible components[7]. The reversible component involves inflammation, indicating that it can be improved by medical intervention. The irreversible component is associated with joint destruction and deformity; this can be ameliorated by surgical treatment or physical therapy. Therefore, care of individual joints is as important as systemic treatment to avoid worse functional outcomes. The influence of joint impairment on functional disability may differ among individual joints. However, only a few studies with relatively small samples have been conducted on the effect of individual joint impairment on functional disability.

We retrospectively investigated the effect of individual joint impairment on functional capacity during a 3-year period using a large observational cohort of Japanese patients with RA.

MATERIALS AND METHODS

Cohort database. We have established an observational cohort of patients with RA who were treated at the Institute of Rheumatology, Tokyo Women's Medical University, beginning in October 2000[8], the Institute Of Rheumatology Rheumatoid Arthritis (IORRA) cohort. All patients with RA diagnosed using American College of Rheumatology criteria[9] were registered, and their clinical information was collected biannually (April and October) when they visited the outpatient clinic; each biannual survey is considered to be a phase. Clinical information consisted of 3 components: (1) physician evaluation, including the number of tender joints, number of swollen joints, and visual analog scale (VAS) score of disease activity (physician VAS); (2) patient information, including VAS for pain (pain VAS), VAS for general health (global VAS), disability level using the Japanese validated version of the Health Assessment Questionnaire (J-HAQ) score[8], comorbidities, and medications taken during the period; and (3) patient laboratory data. Data collected from each component were integrated into 1 database for analysis.

Patients and assessment of joints. A total of 4842 and 5262 patients participated in the April 2004 and April 2007 IORRA phases, respectively. Study subjects included 3457 patients who participated in both these IORRA phases. In those patients, 43 joints were assessed: neck, bilateral shoulders, elbows, wrists, finger proximal interphalangeal (PIP) joints, interphalangeal joints of the thumb, metacarpophalangeal (MCP) joints, hips, knees, ankles, and metatarsophalangeal (MTP) joints.

Statistical analysis. The 43 joints were classified into 10 joint areas: neck, shoulder, elbow, wrist, MCP, PIP, hip, knee, ankle, and MTP. Right and left joints were regarded as a single area. Impairment of each of the 10 joint areas was scored based on the presence of swelling or tenderness: score 0 (no swelling or tenderness in either joint), score 1 (swelling or tenderness in a unilateral joint), and score 2 (swelling or tenderness in bilateral joints).

The change of joint impairment from 2004 to 2007 was evaluated by score change, which was defined as the difference between scores from 2004 and 2007. The score change was categorized into 4 groups: improvement (score change > 0), quiescence [both scores (2004 and 2007) = 0], no improvement [no score change (excluding quiescence)], and worsening (score change < 0). Thus, score change indicates the variation of joint impairment over years. ΔJ-HAQ score was defined as the value of subtracting J-HAQ score in 2007 from that in 2004. To investigate the relative contribution of score change to ΔJ-HAQ score and the effect of score change on ΔJ-HAQ score, we constructed a linear model, which had ΔJ-HAQ score as the objective variable and joint areas as the explanatory variables. The relative contribution of joint impairment to ΔJ-HAQ score was estimated using the analysis of variance table of this model, and the effect of joint impairment on ΔJ-HAQ score was evaluated using the parameter estimates of this model.

RESULTS

The basic characteristics of the 3457 patients who participated in this study are shown in Table 1. The mean age of the 84.6% women and 15.4% men was 57.4 years (range 18.0 to 88.0 yrs). Mean disease duration was 11.3 years (range 0 to 60.0 yrs). Rheumatoid factor positivity was 73.0%. Disease Activity Score 28 (DAS28) and J-HAQ score were 3.42 (range 0.01 to 8.69) and 0.73 (range 0.0 to 3.0), respectively. The data showed that 91.6% of patients were treated with disease-modifying antirheumatic drugs.

The change of joint impairment evaluated by score change of each joint area is indicated in Figure 1. Improvement was most frequently observed in the wrist (22.8%), followed by MCP (17.3%), PIP (16.3%), knee (15.9%), ankle (13.9%), elbow (11.1%), MTP (9.4%), and shoulder (8.4%), while worsening was also most frequently observed in the wrist (14.6%), followed by MCP (13.4%), PIP (10.6%), knee (9.4%), ankle (8.9%), elbow (7.9%), shoulder (6.4%), and MTP (5.0%). The score change in neck or hip was classified as quiescence in most patients. For each joint area, the proportion of patients categorized into the improvement group was higher than that categorized into the worsening group.

Table 1. Baseline characteristics of 3457 patients with rheumatoid arthritis. The mean age of the 84.6% women and 15.4% men was 57.4 years. Mean disease duration was 11.3 years. Rheumatoid factor positivity was 73.0%. DAS28 and J-HAQ scores were 3.42 and 0.73, respectively; 91.6% of patients were treated with disease-modifying antirheumatic drugs.

Characteristic	
Age, yrs, mean (SD)	57.4 (12.5)
Female, %	84.6
Disease duration, yrs, mean (SD)	11.3 (8.5)
Patient pain VAS, mm, mean (SD)	28.7 (25.7)
Patient general VAS, mm, mean (SD)	30.3 (25.0)
Physician general VAS, mm, mean (SD)	14.8 (15.1)
DAS28, mean (SD)	3.42 (1.12)
J-HAQ score, mean (SD)	0.73 (0.74)
CRP, mg/dl, mean (SD)	1.0 (1.5)
ESR, mm/h, mean (SD)	30.7 (21.6)
Rheumatoid factor positivity, %	73.0
DMARD use, %	91.6
Methotrexate use, %	58.5
Methotrexate dosage, mg/week, mean (SD)	6.7 (2.9)
Biologics use, %	0.9
Prednisolone use, %	54
Prednisolone dosage, mg/day, mean (SD)	4.5 (2.7)
NSAID use, %	70.7

VAS: visual analog scale; DAS28: 28-joint Disease Activity Score; J-HAQ: Japanese Health Assessment Questionnaire; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs.

Relative contribution of score change on ΔJ-HAQ score. The major joint areas that most frequently contributed to ΔJ-HAQ score were the wrist (31%), shoulder (21%), knee (13%), and ankle (10%). The effect of score change in small joints (PIP, MCP, and MTP) on ΔJ-HAQ score was modest. Although only a small number of patients showed positive or negative score changes of the neck, such changes showed a relatively large effect on ΔJ-HAQ score (Figure 2).

Effect of score change on ΔJ-HAQ score. The effect of score change on ΔJ-HAQ score was evaluated for the shoulder, wrist, knee, and ankle joint areas. A multivariate analysis showed that worsening compared to improvement of the shoulder, wrist, knee, and ankle related to an increase of 0.18 (95% CI 0.11 to 0.25), 0.17 (95% CI 0.12 to 0.21), 0.13 (95% CI 0.07 to 0.18), and 0.13 (95% CI 0.07 to 0.18) in J-HAQ score, respectively (Table 2). During the study period, wors-

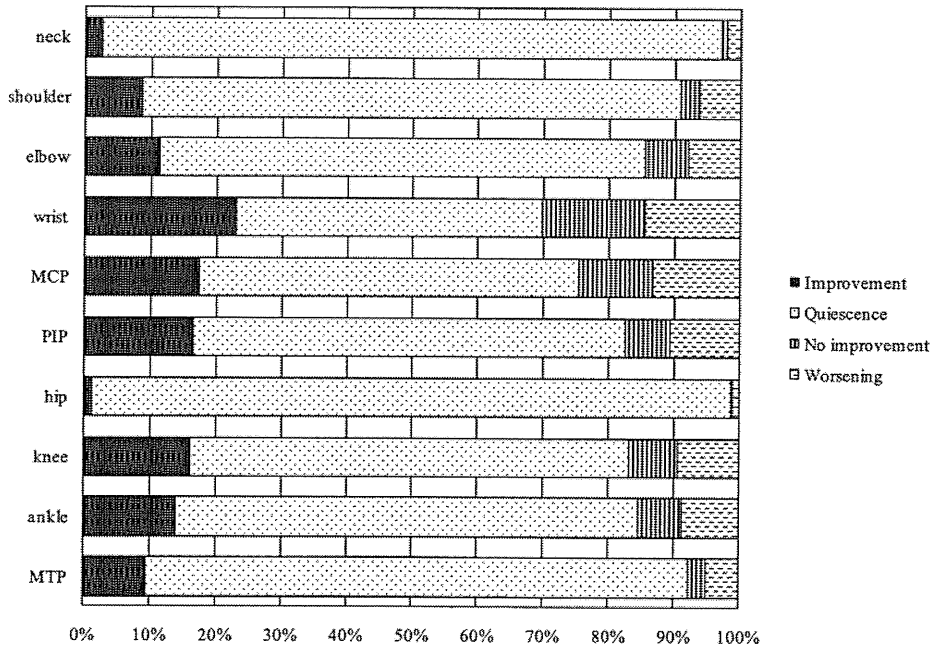

Figure 1. The change of joint impairment from 2004 to 2007 was evaluated by score change, defined as the difference of score of individual joint areas between 2004 and 2007. Score change was categorized into 4 groups: improvement, quiescence, no improvement, and worsening.

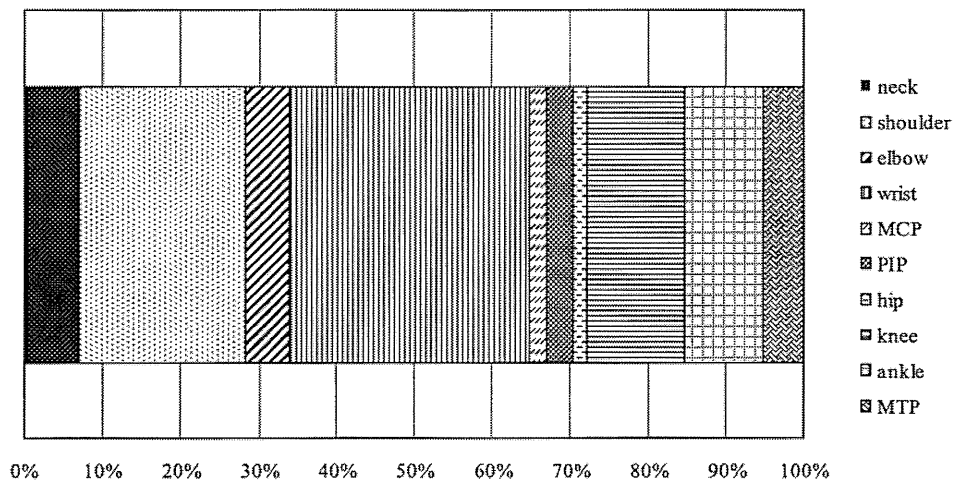

Figure 2. The change of joint impairment from 2004 to 2007 was assessed by score change. ΔJ-HAQ score was defined as the value of subtracting the Japanese Health Assessment Questionnaire (J-HAQ) score in 2007 from that in 2004. The relative contribution of score change to ΔJ-HAQ score was examined using ANOVA.

ening of score change in each joint area was significantly associated with an increase of 0.13 to 0.18 in J-HAQ score.

DISCUSSION

Physical function is involved to some extent in most cases of RA. Suppression or improvement of functional disability is a major goal of RA treatment. HAQ score is the most widely used measure to assess physical function of patients, and J-HAQ score represents the validated Japanese version. In this retrospective study with a 3-year interval, we showed that the wrist, shoulder, knee, and ankle joints made the largest contribution to J-HAQ score change during the 3 years. Previously, our cross-sectional study showed that the shoulder, knee, elbow, wrist, and ankle most commonly contributed to J-HAQ

Table 2. The effect of change in joint impairment on ΔJ-HAQ evaluated by multivariate analysis. The shoulder, wrist, knee, and ankle in the worsening group were associated with a J-HAQ score increase of 0.18, 0.17, 0.13, and 0.13, respectively, compared to the improvement group.

Joint Area	Status of Joint Area, 2004 to 2007*	Estimate (95% CI)	p
Shoulder	Improvement	—	—
	Quiescence	0.06 (0.01–0.11)	0.01
	No improvement	0.10 (0.00–0.20)	0.06
	Worsening	0.18 (0.11–0.25)	< 0.0001
Wrist	Improvement	—	—
	Quiescence	0.04 (0.01–0.08)	0.02
	No improvement	0.04 (–0.01 to 0.08)	0.10
	Worsening	0.17 (0.12–0.21)	< 0.0001
Knee	Improvement	—	—
	Quiescence	0.01 (–0.02 to 0.05)	0.44
	No improvement	0.07 (0.00–0.14)	0.04
	Worsening	0.13 (0.07–0.18)	< 0.0001
Ankle	Improvement	—	—
	Quiescence	0.04 (0.00–0.08)	0.03
	No improvement	0.04 (–0.03 to 0.11)	0.22
	Worsening	0.13 (0.07–0.18)	< 0.0001

* Status of joint area 2004–2007 was evaluated by score change. J-HAQ: Japanese Health Assessment Questionnaire.

score[10]; changes in most of these joint areas were shown to be associated with longterm functional prognosis.

Worsening of arthritis in the shoulder, wrist, knee, and ankle was demonstrated to lead to a 0.13 to 0.18 increase in J-HAQ score as compared to improvement of arthritis in those joints. The mean J-HAQ score of subjects at study entry was 0.73 (SD 0.74; Table 1). The minimally important difference (MID) for HAQ score improvement in RA clinical trials has been reported to range from –0.22 to –0.24[11,12,13]. However, Pope, *et al* showed that the MID of HAQ scores in clinical practice was –0.09 for improvement and 0.15 for worsening[14]. Thus, the 0.13 to 0.18 increases of J-HAQ scores demonstrated in the study deserve attention from a clinical point of view.

Our study revealed that impairment of the shoulder, wrist, knee, and ankle significantly affected functional outcome measured by HAQ score. Recently, a patient-centered approach has been widely applied in RA management[15]. Thus, our study may provide a more efficient guideline for a multidisciplinary RA team that includes rheumatologists, orthopedic surgeons, nurses, and physical and occupational therapists.

To date, only limited studies with relatively small sample sizes have been conducted to address the effect of impairment of individual joints on physical function. The HAQ score has been reported to be associated with radiographic damage of large joints[16]. Our previous cross-sectional study indicated that the shoulder, knee, elbow, wrist, and ankle made the largest contribution to HAQ score[10]. Recently, Häkkinen, *et al* evaluated 66 joints and investigated the associated total and subdimensions of the HAQ score[17]. These authors indicated that range of motion of the wrist, shoulder, and knee is associated with total HAQ score.

The studies described above as well as the current study failed to find any associations between HAQ score and small joints in the hands and feet. In our cross-sectional study[10], the contribution of these small joints to HAQ score was modest. Impairment of small joints can be associated with particular subdimensions of HAQ score, although the previous studies did not indicate such an association in either RA[17] or juvenile idiopathic arthritis[18]. For activities such as dressing, arising, eating, walking, hygiene, reach, and grip, coordination among joints is necessary[18], although the contribution of small joints to these activities may be minor. The relatively large contribution of the neck to ΔJ-HAQ score is of particular interest, because only a small number of patients showed improvement or worsening, suggesting the important role of neck impairment on functional disability (Figure 1).

Our study has some limitations. First, it was not prospective. However, the study has an advantage of analyzing a large database and the effect of improvement or worsening of joint impairment on functional disability during 2 timepoints. Second, of the 4842 patients who participated in the IORRA survey in April 2004, we were unable to collect data for 1385 from the April 2007 survey, for a variety of reasons, including nonparticipation and incomplete data. This may have affected the results. Third, we did not specify the treatments including surgical procedures used during the study period. Therefore, reasons for the improvement or worsening of individual joints were not identified. Fourth, we did not assess range of motion of individual joints because such data were not included in the IORRA database. In some studies, the association of functional disabilities with joint motion was much stronger than that with tender or swollen joint counts[17,19]. In the early stages of RA, joint inflammation has been shown to be associated with functional disability, while loss of joint motion becomes increasingly important in prolonged RA[3,18,19]. However, some prospective studies reported that HAQ score was associated with swollen joint counts[1,17,20]. Other studies have reported an association between joint inflammation and functional disabilities[21,22,23,24]. Moreover, the relationship between joint tenderness or swelling and disabilities is relatively complex. Psychological and social effects and noninflammatory pain may contribute to this complexity.

Our results indicate that impairment of the shoulder, wrist, knee, and ankle joints affects functional capacity. Systemic treatments as well as care of these joints are important to prevent or improve functional disability in patients with RA.

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ORIGINAL ARTICLE

Standard treatment in daily clinical practice for early rheumatoid arthritis improved disease activity from 2001 to 2006

Ayako Nakajima · Eisuke Inoue · Kumi Shidara · Daisuke Hoshi · Eri Sato · Yohei Seto · Eiichi Tanaka · Atsuo Taniguchi · Shigeki Momohara · Hisashi Yamanaka

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Abstract We aimed to clarify the degree of improvement in disease control following early treatment of rheumatoid arthritis (RA) in daily clinical practice in 2006 compared to that in 2001. Using a large observational Japanese RA cohort (IORRA), we analyzed changes in clinical parameters, including disease activity assessed by the disease activity score 28 (DAS28) and physical disability assessed by the Japanese version of the Health Assessment Questionnaire (J-HAQ), which occurred within 2 years of cohort inception. All patients had enrolled in the IORRA cohort within 1 year of RA onset, in either 2001 (2001-cohort) or 2006 (2006-cohort). For both cohorts, changes in clinical features over 2 years were compared by Fisher's exact test or the Wilcoxon test. The 2001-cohort included 71 patients and the 2006-cohort included 56 patients. Over the 2-year period for each cohort, DAS28 significantly decreased from 3.9 to 3.5 in the 2001-cohort ($p < 0.001$) and from 4.1 to 3.1 in the 2006-cohort ($p < 0.0001$), and J-HAQ significantly decreased from 0.62 to 0.49 ($p < 0.02$) in the 2001-cohort and from 0.71 to 0.41 ($p < 0.001$) in the 2006-cohort. Greater improvement in disease activity over 2 years occurred in the 2006-cohort than in the 2001-cohort ($p < 0.05$). Better disease control was obtained following changes in RA treatment strategy that occurred in Japan between 2001 and 2006.

Keywords Disease activity · Inception cohort · Physical function · Treatment · Rheumatoid arthritis

A. Nakajima (✉) · E. Inoue · K. Shidara · D. Hoshi · E. Sato · Y. Seto · E. Tanaka · A. Taniguchi · S. Momohara · H. Yamanaka
Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan
e-mail: ayakonkj@ior.twmu.ac.jp

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, and RA disease activity is associated with a poor prognosis due to an increased incidence of comorbidities such as cardiovascular disease, pulmonary disease, and infection. The life expectancy of patients with RA has been estimated to be 1.2–1.7 times worse than that of the general population [1]. This decreasing mortality is considered to be related to disease activity and physical dysfunction [2, 3]. However, in recent years, the disease activity course in RA patients has been reported to be milder than previously thought [4–6]. The reason for this improvement remains to be elucidated; however, it should be noted that this trend coincides with earlier diagnosis of the disease and more aggressive treatment strategies [2, 3, 7].

Earlier diagnosis and earlier treatment initiation with disease-modifying anti-rheumatic drugs (DMARDs) to ensure tight control of disease activity are crucial in the treatment of RA. Many biologics, such as anti-tumor necrosis factor (TNF) agents [8] and anti-interleukin-6 (IL-6) [9] agents, have been introduced that decrease RA disease activity, even in patients who are resistant to methotrexate (MTX). However, the use of potent immunosuppressive agents and biologics in daily practice is complex, even in patients with active arthritis. Comorbid diseases may prevent patients from using potent immunosuppressive agents or biologics. Furthermore, access to optimal treatment with such agents varies between countries due to differences in indication criteria and health insurance coverage.

In this study, we evaluated the clinical features of Japanese patients with RA who underwent standard treatment, and we examined the contribution of these features to recent advances in the disease control of RA. Patients were selected from a large observational RA cohort (IORRA)

based at the Institute of Rheumatology, Tokyo Women's Medical University, and included patients who experienced the onset of RA within 1 year of either 2001 or 2006.

Patients and methods

Patients

Two groups of patients were selected from the IORRA cohort. The first group (2001-cohort) included patients who enrolled in the IORRA cohort in October 2001 or April 2002 within 1 year of RA onset. The second group (2006-cohort) included patients who enrolled in the IORRA cohort in April 2006 or October 2006 within 1 year of RA onset.

The IORRA cohort was launched in October 2000 as a single institute-based large observational cohort of Japanese RA patients based at the Institute of Rheumatology, Tokyo Women's Medical University (Institute of Rheumatology, Rheumatoid Arthritis). Details about patient enrollment, data collection, and cohort characteristics have been reported previously [10–12]. Various publications have described the features of patients in this cohort, including disease activity [11], gastrointestinal involvement [13], bone fracture [14], arthroplasty [15], depression [10], incidence of tuberculosis [12], and mortality [16]. Briefly, all patients diagnosed with RA were registered in the IORRA cohort after informed consent was obtained, and they were asked to complete and submit a questionnaire sheet at the outpatient clinic biannually (in April and October). Evaluated parameters included patient assessment of pain and global evaluation by the visual analogue scale (VAS), and disability measured by the Japanese Health Assessment Questionnaire (J-HAQ), which was validated in 2003 [17]; physician evaluation of disease activity (swollen joint count, tender joint count, and physician's assessment by VAS); and laboratory parameters. Patients also self-reported the use of various agents, including corticosteroids (frequency and dose converted into prednisolone value) and DMARDs including MTX (frequency and dose). The occurrence of adverse events that had emerged within the previous 6 months was reported voluntarily. Approximately 5,000 patients with RA were involved in each phase of the survey.

Parameters at study entry and at 2 years

In Japan, MTX was officially approved for the treatment of RA in August 1999, and anti-TNF agents were approved in July 2003 (infliximab) and January 2005 (etanercept). Neither tocilizumab nor adalimumab was introduced during this study period. To investigate the effect of standard treatment strategies in patients with early-phase RA, we analyzed the clinical features of RA in two different inception cohorts. Any changes in clinical parameters between baseline and 2 years were compared in both the 2001-cohort and the 2006-cohort, as well as changes being compared between the cohorts.

Statistics

Clinical data at baseline and at 2 years in the 2001-cohort and the 2006-cohort were compared by Fisher's exact test for categorical data and Wilcoxon analysis for consequence data. The differences between the changes from baseline to 2 years between the cohorts were compared by Fisher's exact test for categorical data and Wilcoxon analysis for consequence data. Lost data were compensated for using last observation carried forward (LOCF) analysis.

Results

Changes in demographic features and treatment strategies for early RA in the two cohorts

Seventy-one patients were included in the 2001-cohort and 56 patients were included in the 2006-cohort. The clinical features of each patient cohort are shown in Table 1.

Significant improvement in disease activity, as indicated by the disease activity score (DAS) 28, and physical function, as indicated by the J-HAQ, from baseline to 2 years was observed in both cohorts. In particular, in the 2006-cohort, the mean DAS28 decreased to 3.1, which is categorized as low disease activity, with a 1.0-point reduction of DAS28 from baseline to the end of the 2-year period. In both cohorts, the mean J-HAQ decreased to <0.5, which is categorized as physical remission. The use of DMARDs increased significantly in the 2001-cohort during the 2-year period, whereas the use of DMARDs was already frequent at baseline in the 2006-cohort. Corticosteroid use and dose did not increase in either cohort during either of the 2-year periods, while MTX use and dose increased in both cohorts. No patients in either cohort used biologics at baseline, and only 1.4 and 5.4% of patients in the 2001-cohort and 2006-cohort, respectively, were treated with biologics at 2 years.

The column on the far right in Table 1 shows comparisons of the improvements in clinical features obtained over 2 years between the two cohorts. The degree of improvement in disease activity, indicated by the DAS28, from baseline to 2 years was larger in the 2006-cohort than in the 2001-cohort ($p < 0.032$). The degree of improvement of physical function, indicated by the J-HAQ, from baseline to 2 years was not significantly different between the cohorts; however, in the 2006-cohort the reduction in

Table 1 Comparison of demographic and clinical features of rheumatoid arthritis (RA) patients at baseline and at 2 years in the 2001-cohort and the 2006-cohort

Feature	2001-cohort ($n = 71$)			2006-cohort ($n = 56$)			Difference between cohorts (p value)
	Baseline	2 years later	p value	Baseline	2 years later	p value	
Women (%)	74.7			82.1			
Age (years)	54.7			53.4			
BMI	21.8	22.1	0.095	21.6	21.9	0.183	0.886
DAS28	3.9	3.5	<0.001*	4.1	3.1	<0.001*	0.032**
J-HAQ	0.62	0.49	0.014*	0.71	0.41	<0.001*	0.174
RF-positive (%)	70.1	66.7	0.714	86.5	70.9	0.061	
RF titer (IU/mL)	110.9	128.3	0.035*	108.9	68.2	0.002*	0.281
DMARDs (%)	52.1	70.4	0.038*	83.9	89.3	0.580	
MTX (%)	18.3	40.9	0.005*	46.4	66.1	0.056	
MTX (mg/week)	6.0	7.2	<0.001*	5.7	8.4	<0.001*	0.009**
Biologics (%)	0	1.4	1	0	5.4	0.243	
Corticosteroid (%)	35.2	47.9	0.173	33.9	32.1	1	
Prednisolone (mg/day)	6.5	5.8	0.304	4.8	4.9	0.288	0.788

BMI body mass index, *DAS28* disease activity score 28, *J-HAQ* Japanese version of Health Assessment Questionnaire, *RF* rheumatoid factor, *DMARDs* disease-modifying antirheumatic drugs, *MTX* methotrexate

* Significant difference between baseline and 2 years

** Significant difference between cohorts

mean J-HAQ was 0.30 and the final J-HAQ score was 0.41. The increased dose of MTX during the 2-year period was significantly higher in the 2006-cohort than in the 2001-cohort ($p < 0.009$).

Discussion

As great strides in the treatment of RA have been made in recent years, including the introduction of several biologics and potent immunosuppressive agents, it is important to evaluate the impact of this progress on daily clinical practice. Disease features may be influenced by the timing and type of agents that are introduced in each country. In Japan, MTX was officially approved for the treatment of RA in 1999, and the first anti-TNF agent (infliximab) was approved in 2003. Thus, the features of patients in the 2001-cohort may be considered to reflect treatment strategies used at the dawn of the MTX era, while those of patients in the 2006-cohort reflect both increased experience with MTX and the dawn of the biologics era.

In this study, we demonstrated that in the 2 years after each cohort inception, disease activity and physical function were improved in both cohorts. The improvement of disease activity was more remarkable in the 2006-cohort than in the 2001-cohort: the mean DAS28 decreased by 1.0 point to 3.1 in the 2006-cohort, with this score being categorized as low disease activity with moderate response. The degree of improvement in physical function indicated by the J-HAQ was not significantly different between the cohorts. However, the J-HAQ decreased to 0.41, which is considered to indicate functional remission, in the 2006-cohort, and the 0.30-point J-HAQ reduction observed in the 2006-cohort exceeded 0.22, which is reported to be the minimal clinically important difference that can be demonstrated using an HAQ [18]. Thus, we consider the improvement in physical function obtained in the 2006-cohort to be more clinically meaningful than that obtained in the 2001-cohort. Treatment within the first 2 years of disease activity or responsiveness to treatment may reflect further disease activity and physical dysfunction [2, 7, 19]. Thus, the further improvement in disease activity obtained in recent years in patients with RA may lead to better outcomes, not only with respect to the disease itself but also with respect to comorbidities and mortality.

In the 2006-cohort, MTX was used more frequently at baseline and at higher doses years later, while corticosteroid use either remained constant or tapered. No difference in biologics use was identified in the two cohorts, because the proportion of patients who were treated with biologics during the periods remained low. These results demonstrate that increased use and dosing of MTX, as well as decreased use of corticosteroids, has occurred in daily clinical practice in Japanese RA patients, which represents a very desirable treatment strategy. In the future, intensive treatment, including biologics use, is expected to be increasingly common; thus, substantially better prognoses are anticipated.

In conclusion, using an observational daily practice inception cohort, the present study demonstrated that RA patients with early-phase disease have tended to be treated more intensively and have experienced better control of disease activity in recent years. More intensive treatment, including the use of biologics, is expected to result in better outcomes in patients with RA.

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