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ORIGINAL ARTICLE

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Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan

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Abstract The objective of this study was to show whether the disease activity of rheumatoid arthritis (RA) patients had improved in Japan, and whether the improvement of disease activity had resulted in a better outcome of patients. In a single-institute-based prospective observational cohort of RA patients (Institute of Rheumatology, Rheumatoid Arthritis, IORRA), a total of 7512 patients were enrolled, and their information was collected biannually. A cross-sectional data set A that included all patients in each phase was analyzed. From October 2000 to April 2006, disease activity score DAS28 significantly improved from 4.15 to 3.63, and the frequency of patients in remission (DAS28 < 2.6) increased from 8.5% to 21.5%. During this period, the frequency of methotrexate users increased from 33.9% to 58.7% and the average dosage of methotrexate also increased from 5.59 mg/week to 6.94 mg/week; on the other hand, there was no increase in any adverse reaction among the methotrexate users. To investigate the relationship between longitudinal disease control and progression of disability, a longitudinal data set B that included 712 patients who completed all phases of the study from 2000 to 2006 was selected and was analyzed. The disability index JHAQ of a poorly controlled group (average DAS > 5.1) increased (+34.8%), that of a moderately controlled group (average DAS 3.2–5.1) also increased (+14.0%), but that of a well-controlled group (average DAS < 3.2) decreased (–13.0%). In conclusion, by using a prospective observational cohort IORRA in Japan, we demonstrate that RA disease activity improved from 2000 to 2006, which correlates with an increased use of methotrexate. The suppression of disease activity resulted in a better outcome for patients.

Key words Cohort study · DAS28 · Disability · Methotrexate · Rheumatoid arthritis

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Introduction

The circumstances of patients with rheumatoid arthritis (RA) have dramatically altered in the last 10 years. The introduction of a new class of anti-cytokine drugs has successfully modified the disease course of RA patients with active disease that had not previously been controlled by conventional anti-rheumatic drugs.[1,2] Furthermore, the entire strategy for the treatment of RA has also been altered. Early intervention with anti-rheumatic drugs (disease-modifying anti-rheumatic drugs, DMARDs) was found to result in better responsiveness to the drugs[3–5] and extensive suppression of disease activity led patients to a better outcome.[6,7] As a result, the outcome of RA patients should have become better, and this was shown by the comparison of several cohorts in different years of investigation;[8–13] however, this has not been clearly shown in a Japanese cohort study, where the circumstances in the daily practice of RA is quite different when compared with that in western countries. Especially, it is of interest whether better control of the disease activity of RA patients leads to prevention of long-term disability in Japanese circumstances.

In this article, we clarify the longitudinal improvement of RA patients' outcome, including disease activity, using a single-institute-based large observational cohort in Japan. We also show the importance of suppression of disease activity in the prevention of disability using the same patients.

Patients and methods

We established a prospective observational cohort of RA patients at the Institute of Rheumatology, Tokyo Women's Medical University in October 2000.[14–23] We designate this

cohort as the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) study. Patients with RA who fulfilled the American College of Rheumatology criteria for RA[24] were registered, and their information was collected biannually (April to May and October to November) when the patient visited the outpatient unit of our Institute of Rheumatology for consultation. Informed consent from each patient was routinely taken each time.

Clinical information consisted of three components. The first was the physician's evaluation, which included the number of tender joints, number of swollen joints, and a visual analog scale (VAS) of disease activity rated by the physician. The second was the information collected from the patients, which included VAS for pain, VAS for general health disability level using the Japanese version of the health assessment questionnaire (JHAQ),[14] height, body weight, co-morbidity in the last 6 months, and information on drugs taken during the period. Patients were asked by the attending physician to answer these questions by filling out the questionnaire sheet at home and were instructed to mail it back in a pre-stamped envelope within 2 weeks of their clinic visit. The third part collected laboratory data from patients, including C-reactive protein levels, erythrocyte sedimentation rate (ESR), blood count, transaminases, and urine analysis. All information collected from each section was integrated into one database, and was used for analysis. Disease activity score DAS28 was calculated according to the original method.[25]

A total of 7512 patients were enrolled in this study. In all phases of this study, more than 99% of RA patients in our institute were enrolled and more than 98% of patients answered and mailed their questionnaires back to us. Thus, the patient selection bias is considered to be small, if any. The ethical committee in Tokyo Women's Medical University approved this study.

The improvement of the disease activity was evaluated by the comparison of all patients who were enrolled at each phase of the survey, i.e., a cross-sectional data set, as data set A. To investigate the relationship between longitudinal control of disease activity and progression of disability, a data set B was selected. Data set B included 712 patients who completed all phases of the study (Phase 1: October 2000 to Phase 12: April 2006) and had no missing data concerning their JHAQ and DAS28. Because a certain proportion of patients were lost during follow-up or were newly enrolled in each phase of the study, patients in data set A were not identical from Phases 1 to 12. On the other hand, all patients in data set B were identical from Phases 1 to 12. The distribution of DAS28 in each phase was visualized using the kernel density estimation method.

Results

Characteristics of patients

Table 1 shows the characteristics of patients in data set A. When we compared the measurements between Phase 1 (October 2000) and Phase 12 (April 2006), the average age and the average duration were longer in Phase 12 than in Phase 1.

Improvement of disease activity from 2000 to 2006

Figure 1 shows the distribution of DAS28 in years 1–6 in this cohort. Distribution of DAS28 steadily shifted from the original position to the left over the five years, and the average DAS28 improved from 4.15 ± 1.18 (October 2000) to 3.63 ± 1.21 (October 2004; $P < 0.00001$). As shown in Table 1, all four components of DAS28, that is, tender joint count, swollen joint count, ESR and global health of patient, improved over the five years.

Figure 2 demonstrated the distribution of disease activity on the basis of DAS28- European League Against Rheu-

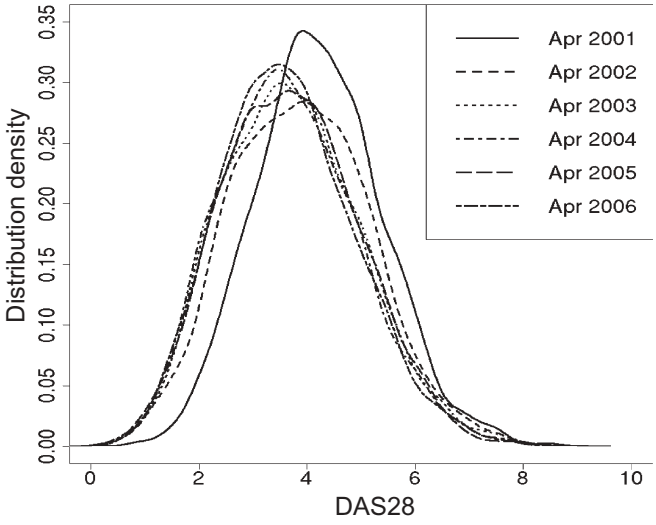

Fig. 1. Distribution of the disease activity score DAS28 in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) cohort. Changes in the distribution of DAS28 in a cross-sectional cohort were demonstrated from Phase 2 (April 2000) to Phase 12 (April 2006)

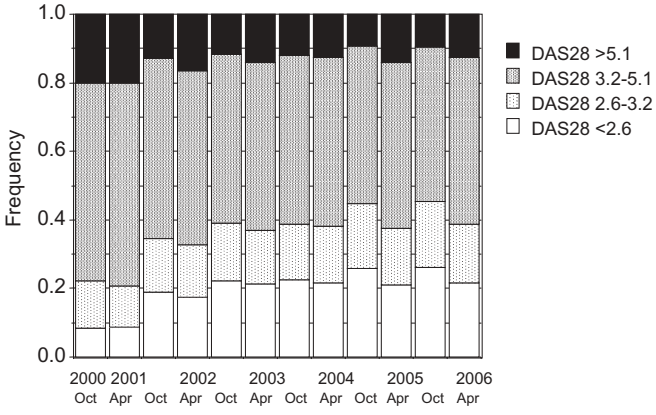

Fig. 2. Distribution of the disease control based on DAS28 in the IORRA cohort. Disease activity of patients was categorized by DAS28 using the established cut-off values, where patients with DAS28 < 2.6 is in remission, and patients with DAS28 < 3.2 is in low disease activity

Table 1. Characteristics of patients in each phase of survey (Data set A)

Phase	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6	Phase 7	Phase 8	Phase 9	Phase 10	Phase 11	Phase 12
Year	2000	2001	2001	2002	2002	2003	2003	2004	2004	2005	2005	2006
Month	October	April	October	April	October	April	October	April	October	April	October	April
n	3945	3831	4333	4794	4942	5048	4632	4728	4837	4841	4838	4933
Female (%)	82.36	82.48	82.60	82.54	82.84	82.67	82.97	83.33	83.50	83.70	83.84	84.09
Age (years)	57.08	57.58	57.49	57.62	57.76	58.00	57.98	58.25	58.21	58.50	58.47	58.65
Duration (years)	9.96	10.17	10.44	10.62	10.89	11.19	11.20	11.33	11.48	11.73	11.94	12.03
Height (cm)	156.45	156.36	156.47	156.60	156.58	156.66	156.67	156.66	156.70	156.75	156.76	156.84
Weight (kg)	52.47	52.52	52.51	52.82	52.78	52.84	52.86	53.03	52.89	52.93	52.85	53.03
BMI	21.39	21.45	21.42	21.50	21.48	21.49	21.49	21.56	21.49	21.50	21.46	21.51
DAS28	4.15	4.22	3.70	3.88	3.62	3.72	3.59	3.65	3.45	3.70	3.45	3.63
DAS28–CRP	3.51	3.58	3.08	3.26	3.00	3.14	2.97	3.04	2.85	2.99	2.76	2.87
JHAQ	0.80	0.82	0.76	0.80	0.79	0.81	0.79	0.81	0.77	0.80	0.76	0.78
TJC (28)	3.24	3.19	2.11	2.54	1.98	2.29	2.04	2.22	1.92	2.14	1.78	2.09
SJC (28)	3.21	3.15	2.27	2.75	2.39	2.55	2.16	2.33	1.90	2.27	1.74	1.98
Pain VAS	33.31	36.13	32.17	34.83	30.74	33.41	31.26	32.92	29.79	32.56	28.71	31.94
General VAS	35.04	37.58	33.80	36.81	32.22	34.95	32.66	34.56	31.32	34.06	30.56	33.32
Physician VAS	26.44	25.37	19.93	19.08	16.68	17.20	16.03	16.83	15.00	16.40	14.47	14.94
CRP (mg/dl)	1.43	1.59	1.33	1.39	1.25	1.38	1.25	1.27	1.07	1.16	0.99	0.99
ESR (mm/h)	37.46	38.85	35.40	36.02	34.58	34.59	34.50	34.38	31.88	37.15	33.87	36.53
Remission (%)	8.54	8.69	19.07	17.35	22.11	21.19	22.56	21.69	25.80	21.09	25.98	21.53
Low disease activity (%)	22.24	20.84	34.47	32.81	39.09	36.90	38.87	38.16	44.60	37.56	45.37	38.79
Methotrexate dosage (mg/week)	5.59	5.86	5.98	6.13	6.27	6.35	6.50	6.55	6.64	6.75	6.90	6.94
Prednisolone dosage (mg/day)	5.01	4.57	4.52	4.64	4.62	4.72	4.62	4.61	4.60	4.55	4.50	4.51
NSAIDs (%)	70.67	74.03	72.07	71.09	69.47	68.58	69.43	69.35	69.34	67.75	68.44	67.93
DMARDs (%)	82.18	85.51	86.52	84.98	85.96	85.68	87.05	87.88	89.75	88.97	90.51	89.60
Corticosteroids (%)	48.21	51.47	51.07	50.13	51.36	51.84	52.55	52.86	54.31	53.27	53.60	53.13
Biologics (%)	–	–	–	–	–	–	0.09	0.49	0.93	1.20	2.36	2.88
Methotrexate (%)	33.92	39.81	41.56	41.61	43.57	45.40	49.14	51.46	54.95	55.84	58.54	58.65
Infliximab (%)	–	–	–	–	–	–	0.09	0.49	0.93	1.20	1.69	1.91
Etanercept (%)	–	–	–	–	–	–	–	–	–	–	0.66	0.97

BMI, body mass index; DAS28, disease activity score; CRP, C-reactive protein; JHAQ, the Japanese version of the health assessment questionnaire; TJC, tender joint count; SJC, swollen joint count; VAS, visual analog scale; ESR, erythrocyte sedimentation rate; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs

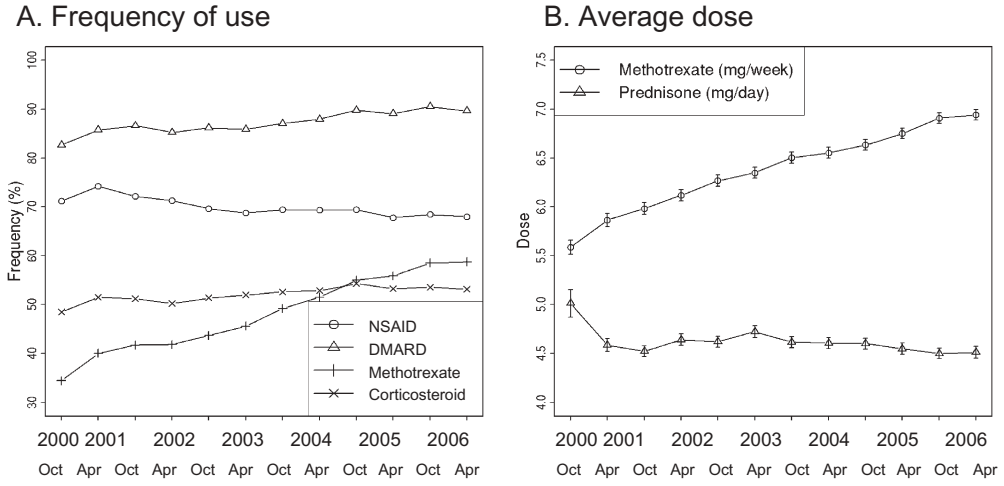

Fig. 3. Use of therapeutic medications in the IORRA cohort. **A** Changes in the frequencies of each class of medication used in a cross-sectional cohort were demonstrated from Phase 1 (October 2000) to Phase 12 (April 2006). NSAIDs (*circles*), DMARD (*triangles*), methotrexate (*plus symbols*), and corticosteroid (*crossmarks*). **B** Changes in the average dosage of methotrexate (*circles*) and prednisolone (*triangles*) used in a cross-sectional cohort were demonstrated from Phase 1 (October 2000) to Phase 12 (April 2006). *NSAID* nonsteroidal anti-inflammatory drugs; *DMARD* disease-modifying anti-rheumatic drugs

matism (EULAR) criteria.[25] The frequency of patients in remission defined by DAS28 < 2.6 increased from 8.5% to 21.5%, those in low disease activity defined by DAS28 < 3.2 also increased from 22.2% to 38.8%.

Changes in medication rate of various drugs for the treatment of RA

We compared the rate of patients taking various medications during this period. Patients who took DMARDs (82%–90%), oral corticosteroid (48%–53%), have increased. On the other hand, those who took nonsteroidal anti-inflammatory drugs slightly decreased (71%–68%, Table 1, Fig. 3). The percentages of patients who took biologics including infliximab and etanercept were still small even in April 2006 (2.9%). The most striking changes were seen in methotrexate usage. The rate of methotrexate users increased markedly (34%–59%). The average dosages of methotrexate and prednisolone were also analyzed. The average dosage of methotrexate increased significantly (5.59–6.94 mg/week), whereas that of prednisolone decreased (5.01–4.51 mg/day). It is of concern that the increased use of methotrexate might increase the adverse reactions. However, the frequency of patient-reported side effects, that of white blood cell <3000 mm^3, and that of alanine aminotransferase >90 IU/l among patients taking methotrexate did not increase during the same period (Fig. 4). Thus, from these notions, the changes in the therapeutic strategy have contributed to a better outcome of RA patients.

Relationship of average DAS28 in four years and progression of JHAQ

We investigated the relationship between the average DAS28 and the progression of JHAQ during the four years. In this analysis, it was necessary to investigate the changes of JHAQ and DAS28 serially in the same patient; thus, data set B was used for the analysis.

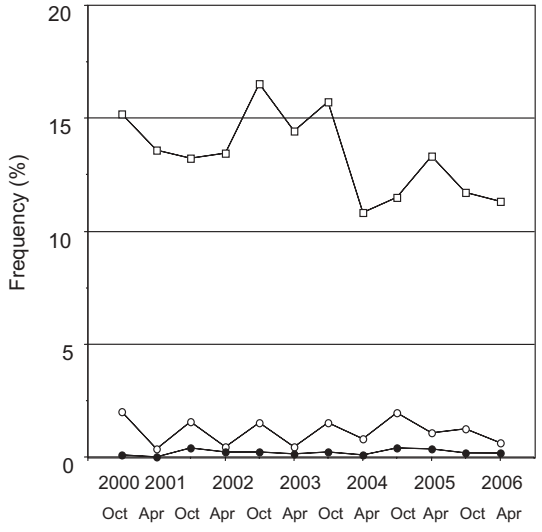

Fig. 4. Frequencies of side effects in the IORRA cohort. Changes in the frequencies of patient-reported side effects (*squares*), white blood cell <3000 mm^3 (*filled circles*), alanine aminotransferase >90 IU/l (*open circles*) were demonstrated from Phase 1 (October 2000) to Phase 12 (April 2006)

Patients were stratified according to their average DAS28 over four years into three groups, i.e., a poorly controlled group (average DAS > 5.1, n = 59), a moderately controlled group (average DAS 3.2–5.1, n = 469), and a well-controlled group (average DAS < 3.2, n = 184). The baseline characteristics of the patients in each group are listed in Table 2, and the progression of JHAQ in each group is shown in Fig. 5. Although the baseline JHAQ was different in these three groups, JHAQ increased steadily from 1.32 to 1.78 in the poorly controlled group (+34.8%) and 0.86 to 1.00 in the moderately controlled group (+14.0%), but JHAQ decreased from 0.46 to 0.40 (–13.0%) in the well-controlled group of RA patients. Statistical analysis using the Jonckheere test demonstrated statistically significant increase of disability in the poorly controlled group (P = 0.0000005368) and in the moderately controlled group (P = 0.0007197), but not in the well-controlled group (P = 0.9918), indicating a direct link between average

Table 2. Baseline characteristics of patients in data set B

	All		DAS28 < 3.2		DAS28 3.2–5.1		DAS28 > 5.1		
N	712		184		469		59		Test
Female (%)	86.66		77.71		89.55		91.53		0.109491438
NSAIDs (%)	78.37		73.91		78.89		88.14		0.46356324
DMARDs (%)	91.01		91.30		90.83		91.53		0.950195687
MTX (%)	45.22		39.67		46.70		50.85		0.136228541
Steroids (%)	52.95		41.85		56.08		62.71		0.006978141
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Test
Age	56.22	10.78	55.46	11.53	56.24	10.51	58.44	10.30	0.192575633
Duration	9.30	8.00	8.51	8.10	9.39	7.99	11.07	7.53	0.018003098
DAS28	4.21	1.15	3.36	0.93	4.36	0.96	5.67	1.19	2.87×10^{-41}
JHAQ	0.80	0.69	0.46	0.51	0.86	0.69	1.32	0.69	9.63×10^{-19}
TJC28	3.31	3.99	1.83	2.15	3.26	3.68	8.37	6.19	2.28×10^{-19}
SJC28	3.48	3.72	2.41	2.55	3.53	3.55	6.41	5.96	6.40×10^{-9}
Pain VAS	34.85	24.17	24.33	21.39	36.67	23.61	53.32	22.18	1.29×10^{-17}
General VAS	35.55	22.75	25.51	20.03	37.34	22.28	52.58	20.83	1.21×10^{-16}
Physician VAS	29.39	19.77	21.65	15.66	30.40	19.59	45.22	21.54	8.77×10^{-15}
CRP (mg/dl)	1.60	2.08	1.03	1.74	1.60	1.90	3.40	3.17	1.45×10^{-13}
ESR (mm/h)	40.17	24.58	24.43	17.19	43.53	23.25	62.57	26.92	1.84×10^{-31}
MTX dosage (mg/week)	5.86	2.61	6.30	3.12	5.85	2.45	4.84	2.09	0.095247821
Prednisolone dosage (mg/day)	4.86	7.82	4.01	1.80	5.09	9.26	4.94	2.01	0.041097985

MTX, methotrexate

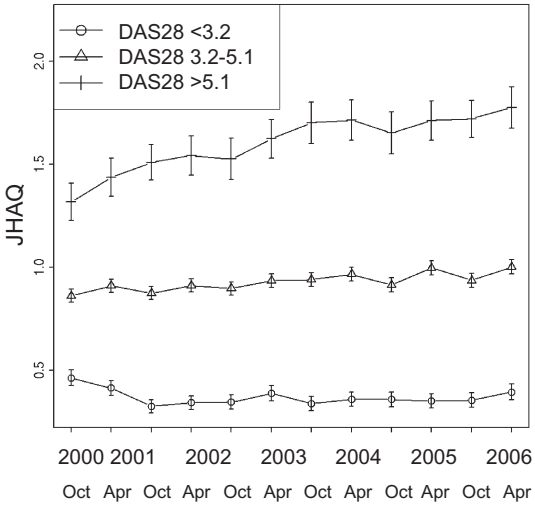

Fig. 5. Progression of disability in longitudinal analysis in the IORRA cohort. By the analysis of 712 patients in data set B, progression of disability assessed by the Japanese version of the health assessment questionnaire was demonstrated in rheumatoid arthritis patients whose average DAS28 in 5 years of investigation was >5.1 (*plus symbols*), 3.2–5.1 (*triangles*), and <3.2 (*circles*). Patients with active disease showed progression of disability whereas those with inactive disease did not develop the disability

disease activity during the five years and progression of disability in RA patients.

Discussion

Using a prospective observational cohort IORRA in Japan, we clearly demonstrated (1) an improvement of disease activity of RA patients over the past 5 years, (2) that a higher dosage of methotrexate is suspected to contribute mainly to the suppression of disease activity, and (3) that suppression of disease activity resulted in better patient outcomes assessed by JHAQ. A large number of patients who were registered and followed longitudinally with a carefully designed protocol enabled us to draw these conclusions.

DAS28 is a composite scoring system for disease activity derived from physician evaluations, clinical data, and patient feedback; thus, it is suitable to assess disease activity objectively. We have shown that the average DAS28 was improved, all the four components of DAS28 were improved, and the disease activity assessed by DAS28-EULAR criteria was also improved. Thus, the improvement of disease activity of patients with RA in this observational cohort is quite significant.

In Japan, infliximab was approved for RA in July 2003, and etanercept was launched in March 2005.[26] The number of infliximab users in Phase 12, the last stage of this study, was 94 (1.91%), and that of etanercept users was 46 (0.97%). Because this study was started in 2000, it represents basically clinical results from the pre-anti- tumor necrosis factor (TNF) era in Japan. Even in these circumstances, significant improvement of disease activity based on DAS 28 was clearly demonstrated in our observational cohort of RA patients. According to the significant increase in both the frequency of use and dosage of methotrexate, the contribution of methotrexate is the most likely cause for the improvement of DAS28. This is reasonable since the consensus among rheumatologists was that methotrexate was the standard drug[27] in the pre-anti-TNF era. Considering the powerful anti-rheumatic effects of infliximab and etanercept, the disease activity of our RA patients will be improving by the increasing use of these biologics in our daily practice in the near future.

One may think that the dosage of methotrexate used in this study was low, but the maximum dosage of methotrexate is regulated by the Japanese government and is limited to 8 mg/week. This dosage of methotrexate is not sufficient to suppress disease activity of most RA patients; however, our study also demonstrated the dosage-dependent effect of methotrexate in the noninterventional observation cohort. In addition, we would like to stress that the information in the IORRA study is essentially based on the patients' self-reports; thus the dosage of each medication represents actual conditions in practice.

Although the baseline characteristics of the patients were different, good control of disease activity successfully kept patients from disability, whereas poor control of disease activity resulted in the progression of the disability. It should be emphasized that patients with moderate disease activity (DAS 28 3.2–5.1) still showed considerable progression of disability 5 years later. Also, two-thirds of our patients (469 out of 712) belonged to this group, suggesting that our overall clinical practice has not reached a satisfactory level. This is consistent with the recent report that claimed RA patients with stable, long-standing disease continued to deteriorate despite intensified treatment with traditional anti-rheumatic drugs.[28] The relationship between DAS28 and JHAQ progression should be investigated more precisely because at the entry into this study the three groups of patients displayed different stages of the disease. However, our data suggested that we have to control the disease activity of RA patients more strictly. A "treat-to-target" strategy should be undertaken in the management of RA in daily practice, and from our results, a target DAS28 should be less than at least 3.2 to prevent the progression of disability. From this aspect, it is noteworthy that the percentage of patients who are in low disease activity (DAS28 < 3.2) increased from 22.2% in 2000 to 38.8% in 2006. Thus, we believe that "treat to target" is a quite realistic concept in the daily practice of rheumatology.

A limitation of this study is the possible presence of bias derived from the intrinsic nature of this observational study. One may criticize possible institutional bias given that this study is a single-institutional study. However, our institute is the largest clinical center for RA patients in Tokyo, where people from every part of Japan live, and that our cohort registered more than 1% of the total RA patients in Japan, the institutional bias should be minimal, if any. Furthermore, our study excluded the selection bias as much as possible. Actually, more than 99% of RA patients who visited our institute during the study period were registered, and more than 98% of patients returned the questionnaire sheet.

At each phase of our study, approximately 10% of patients were newly registered whereas approximately 10% of patients left our registry. Because our institute is located in the center of Tokyo, many patients with RA may travel long distances. The purpose of their visit may be to obtain a second opinion for therapeutic strategy, and thus they may not keep visiting us thereafter. However, it is our principle to enroll all patients with RA in this cohort and thus we may lose many patients during follow-up. Also, we sometimes refer patients with RA to their family doctors, who may lose them during follow-up. Thus, the cohort of data set A is composed of different patients. On the other hand, we have used data set B where all patients completed all the survey Phases from 1 to 12 and there were no missing data on DAS28 and JHAQ. Thus we have used these two data sets according to the purpose of the analysis to reduce the possible bias.

In conclusion, the disease activity of RA patients in our Japanese cohort has improved significantly from 2000 to 2006, and the higher dosage of methotrexate has made a significant contribution to this phenomenon. Furthermore, the average DAS28 in this period was able to chart the progression of disability assessed by JHAQ quite effectively. In a "treat-to-target" therapeutic strategy, the target DAS28 should be less than 3.2 to prevent progression of disability and to provide considerable benefits to RA patients.

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