Table 2 Correlations between organ involvement and sex or skin involvement in all 405 SSc patients

Organ involvement	Sex (% of each sex)			Skin involvement (% of each type)		
No. of cases (%) (n = 405)	Female (n = 376)	Male (n = 29) RR, 95% CI (vs. female)	P value	lSSc (n = 270)	dSSc (n = 135) RR, 95% CI (vs. lSSc)	P value
GI tract	175 (46.5)	12 (41.4)	0.7001	107 (39.6)	80 (59.3)	0.0002
187 (46.2%)		0.81, 0.37–1.7			2.2, 1.5–3.4	
Lung	182 (48.4)	22 (75.9)	0.0061	108 (40.0)	96 (71.1)	<0.0001
204 (50.4%)		3.4, 1.5–8.6			3.7, 2.4–5.8	
Heart	72 (19.2)	7 (24.1)	0.4737	35 (13.0)	44 (32.6)	<0.0001
79 (19.5%)		1.3, 0.51–3.1			3.2, 2.0–5.4	
Kidney	56 (14.9)	4 (13.8)	1	29 (10.7)	31 (23.0)	0.0017
60 (14.8%)		0.91, 0.26–2.5			2.5, 1.4–4.3	
SRC	10 (2.7)	3 (10.3)	0.0581	2 (0.74)	11 (8.2)	0.0002
13 (3.2%)		4.2, 0.91–15			12, 3.1–78	
PAH	60 (16.0)	5 (17.2)	0.7956	39 (14.4)	26 (19.3)	0.2505
65 (16.0%)		1.1, 0.36–2.8			1.4, 0.81–2.4	

GI gastrointestinal, *SRC* scleroderma renal crisis, *PAH* pulmonary arterial hypertension, *RR* relative risk, *CI* confidence interval

Table 3 Correlations between organ involvements

	GI tract					
Lung	0.1351	Lung				
	1.4 (0.92–2.0)					
Heart	0.001	<0.0001	Heart			
	2.4 (1.4–4.0)	4.7 (2.7–8.7)				
Kidney	0.6754	0.0076	0.0003	Kidney		
	0.87 (0.50–1.5)	2.2 (1.3–4.0)	3.2 (1.8–5.8)			
SRC	0.2748	NA	<0.0001	NA	SRC	
	1.9 (0.62–6.4)		16 (4.6–71)			
PAH	0.5906	<0.0001	<0.0001	0.8504	0.1393	PAH
	1.2 (0.68–2.0)	4.0 (2.2–7.7)	3.9 (2.2–7.0)	1.1 (0.48–2.1)	2.4 (0.64–7.7)	

The upper tier indicates P value and the lower tier relative risk (95% confidence interval)

NA means not applicable because of the small number of patients. *GI* gastrointestinal, *SRC* scleroderma renal crisis, *PAH* pulmonary arterial hypertension

P = 0.0096). In contrast, the SSc–Sjögren overlap syndrome had a significant negative correlation with lung (RR 0.40; 95% CI 0.21–0.74; P = 0.0042) or heart involvement (RR 0.072; 95% CI 0.0040–0.34; P = 0.0002). Patients with the SSc–SLE overlap syndrome also had significantly less GI involvement than those without this syndrome (RR 0.35; 95% CI 0.11–0.91; P = 0.0425). Overlap with RA or myositis was not associated with organ involvement. Except for two males with myositis, the SSc patients with overlapping CTD were all female. A significant excess of females was found only with the SSc–Sjögren overlap syndrome (P = 0.0365).

Autoantibody subsets

The 357 patients (330 females [92.4%] and 27 males [7.6%]), who were examined for ANA and the three anti-ENA antibodies were included in the analysis of autoantibody subsets. As shown in Fig. 2, most of the patients

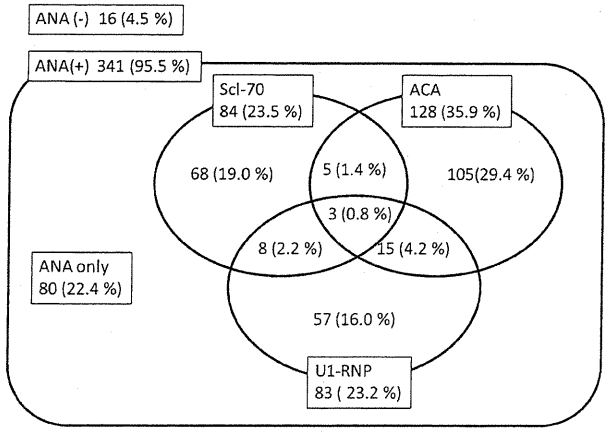

Fig. 2 Numbers and ratios of autoantibody subsets in 357 SSc patients who were examined for ANA and the three anti-extractable nuclear antigens (anti-ENA) antibodies. *ANA* antinuclear antibody, *Scl-70* anti-Scl-70 antibody, *ACA* anti-centromere antibody, *U1-RNP* anti-U1-RNP antibody

(341; 95.5%) were positive for ANA. In addition to ANA, 31 patients (8.7%) had two or all three (multiple) anti-ENA antibodies simultaneously. Among patients with multiple anti-ENA antibodies, the majority had the combination of anti-centromere and anti-U1-RNP antibodies ($n = 15$, 4.2% of 357 patients). No significant correlation was found between sex and the antibody subsets.

Skin involvement and autoantibodies

Of the 357 SSc patients with analysis of antibodies as described above, 126 patients (35.3%) had dSSc and 231 patients (64.7%) had lSSc. Among the 126 patients with dSSc, 56 (44.4%) had anti-Scl-70, 14 (11.1%) had anti-centromere antibody, and 26 (20.6%) had anti-U1-RNP antibody. On the other hand, among the 229 patients with lSSc, 28 (12.2%) had anti-Scl-70, 114 (50.0%) had anti-centromere antibody, and 57 (24.9%) had anti-U1-RNP antibody.

Conversely, of the 84 patients who were positive for anti-Scl-70 antibody, 56 (66.7%) had dSSc and the others had lSSc. Among the 128 patients with anti-centromere antibody and the 83 patients with anti-U1-RNP antibody, 114 (89.0%) and 57 (68.7%), respectively, had lSSc. It was confirmed that patients who had anti-Scl-70 antibody were more likely to have dSSc (RR 5.8; 95% CI 3.4–10; $P < 0.0001$), while those with anti-centromere antibody were more likely to have lSSc (RR 7.8; 95% CI 4.3–15; $P < 0.0001$). Anti-U1-RNP antibody was not associated with the type of skin involvement ($P = 0.4328$). Also, in patients with multiple anti-ENA antibodies, this showed no significant association with the type of skin involvement.

Organ involvement and autoantibodies

Table 4 demonstrates correlations (using the χ^2 test) between 4 groups stratified by the presence of anti-ENA antibodies (each antibody alone and multiple antibodies) and each organ involvement in the 357 SSc patients who were examined for the three anti-ENA antibodies. Patients without the anti-ENA antibody were excluded. The rates of organ involvement among the 357 patients with analysis of antibodies were analogous to those for the entire patient population. Comparisons between the 4 groups revealed that patients with anti-Scl-70 antibody alone had a significantly increased risk of lung (RR 12, $P < 0.0001$) or heart involvement (RR 3.5, $P = 0.0137$), while patients with anti-centromere antibody alone had a significantly decreased risk of involvement of these organs (RR 0.048 or 0.12, $P < 0.0001$ or $P = 0.0011$, respectively) or kidneys

Table 4 Correlations between autoantibodies and organ involvement in 357 SSc patients

Organ involvement No. of cases (%) ($n = 357$) *P* value RR (95% CI)	Only anti-Scl-70 antibody ($n = 68$) No. of cases	Only anti-centromere antibody ($n = 105$)	Only anti-U1-RNP antibody ($n = 57$)	Multiple anti-ENA antibodies ($n = 31$)
GI tract	35	48	24	21
170 (47.6%)	0.833	0.3422	0.1686	0.0229
	1.1 (0.46–2.6)	0.69 (0.32–1.5)	0.52 (0.20–1.3)	4.3 (1.3–16)
Lung	55	22	34	15
186 (52.1%)	<0.0001	<0.0001	0.4118	0.4044
	12 (4.4–37)	0.048 (0.019–0.11)	1.5 (0.58–3.9)	0.60 (0.18–2.0)
Heart	21	8	14	5
72 (20.2%)	0.0137	0.0011	0.2717	0.5992
	3.5 (1.3–9.5)	0.12 (0.030–0.39)	1.9 (1.3–9.5)	0.65 (0.11–2.9)
Kidney	9	7	8	6
47 (13.2%)	0.9476	0.0244	0.8908	0.2682
	0.96 (0.25–3.2)	0.21 (0.048–0.75)	1.1 (0.26–3.9)	2.4 (0.45–10)
SRC	3	0	2	0
10 (2.8%)	0.9283	0.9491	0.9321	0.9698
	–	–	–	–
PAH	12	8	16	7
60 (16.8%)	0.9764	0.0034	0.0267	0.3865
	1.0 (0.31–3.0)	0.15 (0.038–0.49)	3.4 (1.1–9.7)	1.9 (0.40–7.4)

The number of patients with SRC was too small to calculate relative risk

GI gastrointestinal, *SRC* scleroderma renal crisis, *PAH* pulmonary arterial hypertension, *RR* relative risk, *CI* confidence interval, *ENA* extractable nuclear antigens

(RR 0.21, $P = 0.0244$). Additionally, patients with anti-centromere antibody alone also had a significantly lower risk of PAH (RR 0.15, $P = 0.0034$) and none had SRC. On the other hand, patients with anti-U1-RNP antibody had no association with any organ involvement, except for PAH (RR 3.4, $P = 0.0267$). Multiple anti-ENA antibodies were found in 31 patients and showed a significant association with GI involvement (RR 4.3, $P = 0.0229$).

Overlap of CTD and autoantibodies

Among the 357 SSc patients with analysis of antibodies, 44 (12.3%) had Sjögren's syndrome, 17 (4.8%) had SLE or myositis, and 14 (3.9%) had RA. SSc with Sjögren's syndrome was significantly associated with the presence of anti-centromere antibody (RR 3.0; 95% CI 1.6–5.8; $P = 0.0012$). SSc patients with anti-Scl-70 antibody tended to have no overlapping CTD (RR 0.49; 95% CI 0.24–0.93; $P = 0.0374$), in contrast to those with anti-U1-RNP, who were apt to have one or more overlapping CTD (RR 2.5; 95% CI 1.4–4.3; $P = 0.0015$), especially SLE (RR 13; 95% CI 4.3–46, $P < 0.0001$). Patients with multiple anti-ENA antibodies showed no significant associations with overlap of CTD.

Discussion

This was a retrospective cohort study of SSc patients at a single institution in Japan, conducted to clarify the clinical features of SSc, especially the association of clinical manifestations with antibody subsets. In addition to being ethnically homogeneous, the large number of subjects in this study ($n = 405$) supports the idea that this cohort represents an overview of the Japanese SSc population. We focused on the presence or absence of organ involvement and autoantibodies for SSc because they can be markers for several phenotypes of SSc, and are useful for making diagnostic, therapeutic, and prognostic decisions even at an early stage of the disease. Further, our study also included patients who had only bilateral symmetrical sclerodactyly, which made it possible to include patients with mild or early SSc in the investigation, showing heterogeneous manifestations of SSc.

The female-to-male ratios of SSc patients differ among various studies, but a female excess is a consistent finding. In the present study, the percentage of males with SSc was relatively low (7.2%) compared with that in recent Japanese (14.8%, $n = 203$) [19] and international (19.8%, $n = 1{,}645$) [20] studies. However, we found a statistically significant increase in the percentage of males with SSc in our more recent cohort, from 3.9% (up to 1989) to 10.6% (from 1990 onward). Indeed, a previous Japanese study of SSc in patients with the onset before 1988 also showed a low percentage of males (6.4%, $n = 636$) [21]. This supports the hypothesis that the sex ratio of Japanese SSc patients has been changing recently with an increase in the number of male patients. The reason is unclear. For one thing, the sex ratio of populations varies from region to region and from country to country and it also varies with the times, and for another a study of monozygotic and dizygotic twins concluded that multiple factors, including environmental ones and/or acquired genetic alterations, might play a significant role in the incidence of SSc [22]. Further detailed regional epidemiological studies including environmental factors would be required to understand the relation between sex and CTDs such as SSc.

Male gender and lSSc were found to be factors for a later onset of SSc in our present study, but other studies have not detected a significant relation between the age at onset and sex [23] or the type of skin involvement [24]. Age at onset of SSc varies by ethnicity and sex [23]. In addition to the poor prognosis [7], the later onset in Japanese men with SSc resulted in shorter disease duration for males compared with females, which may be one of the characteristics of Japanese patients with SSc.

The prevalence of organ involvement varies markedly between reports because of differences in the ethnic backgrounds and the definitions employed, whereas the ratio of dSSc to lSSc is similar in most reports. We did not detect an increase in the prevalence of organ involvement related to the duration of SSc. This supports the concept that organ involvement in SSc does not increase year by year, but rather develops in a few years after onset [25, 26]. Generally, SRC occurs in about 10% of SSc patients; especially, those who have dSSc with a disease duration of under 4 years show an elevated risk of SRC [27]. Nevertheless, we found a low prevalence of SRC (3.2%) similar to prevalences in previous Japanese reports (4–5%) [28, 29] and that in a recent study (1.5%) [19]. Ethnic factors might contribute to the low prevalence of SRC in Japan, as they do to the high prevalence of malignant hypertension in blacks [30].

In the present study most organ involvement, except for PAH, was significantly associated with dSSc, as was also shown in a previous study [26]; also, the prevalence of organ involvement mostly corresponded with that in a previous Japanese study [21]. PAH was significantly correlated with lung involvement, namely interstitial lung disease (ILD), but this does not mean that ILD always causes PAH. We cannot discuss the relation between ILD-related and unrelated PAH, because we do not have respiratory function test data. Positive correlations between organ involvements (Table 3) just imply that patients with severe SSc have several organ involvements simultaneously.

Of the 405 SSc patients, we investigated 357 for ANA and anti-ENA antibodies including anti-Scl-70, anti-U1-RNP, and anti-centromere antibodies. These autoantibodies were chosen because they have been commonly measured in SSc patients and the tests are approved by the Japanese national health insurance system. The percentage of patients who had each antibody was mostly the same as the data in a report by Steen ($n = 1,432$) [3]. It has been confirmed that anti-Scl-70 antibody was associated with dSSc and anti-centromere antibody with lSSc, while anti-U1-RNP antibody was not related to the type of skin involvement [31]. As indicated by previous reports on the relation between the anti-ENA antibodies and organ involvement, our results confirmed that anti-Scl-70 antibody was correlated with lung or heart involvement [3], and that anti-centromere antibody was inversely correlated with organ involvement, except for GI involvement [4]. These results contribute to a poor prognosis for patients with anti-Scl-70 antibody and a good prognosis for those with anti-centromere antibody [7].

The significant association shown between anti-U1-RNP antibody and PAH (Table 4) agreed with a previous report by Kuwana et al. [32], but not with a United States study that detected a significant association between anti-centromere antibody and PAH [3]. This discrepancy may be due to different rates of anti-U1-RNP antibody positivity among the studies. Kuwana et al. [32] detected anti-U1-RNP antibody in 27.2% of SSc patients and we did so in 23.2%, whereas Steen found anti-U1-RNP antibody in only 5.0% [3]. Anti-U1-RNP antibody is a characteristic of MCTD, which has the features of SLE, myositis, and SSc. PAH is a common complication in patients with MCTD. Because SSc is sometimes hard to distinguish from MCTD and a diagnosis of MCTD can be changed to SSc [33, 34], a significant association between anti-U1-RNP antibody and PAH in patients with SSc is reasonable.

The reported prevalence of Sjögren's syndrome in SSc patients varies from 5 to 90%, depending on the criteria used, while with salivary gland biopsy 29% of SSc patients were described to have Sjögren's syndrome [35]. In the present study, Sjögren's syndrome was the most common CTD that overlapped with SSc, and the prevalence of this overlap syndrome was 12.6%. We also found that SSc–Sjögren overlap syndrome was associated with lSSc, anti-centromere antibody, overlapping SLE, and less lung or heart involvement. Therefore, in patients with SSc–Sjögren overlap syndrome, attention should be paid to the possibility of overlapping SLE.

In conclusion, we investigated SSc in a cohort of Japanese patients in terms of organ involvement and autoantibodies; our study provided several novel findings, as well as confirming some findings of previous studies. These results represent the characteristics of Japanese SSc patients and could be helpful in elucidating the pathogenesis of SSc.

Conflict of interest None.

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ORIGINAL ARTICLE

Structural damages disturb functional improvement in patients with rheumatoid arthritis treated with etanercept

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Abstract Tumor necrosis factor (TNF) inhibitors have produced improvements in clinical, radiographic, and functional outcomes in rheumatoid arthritis (RA) patients. However, it remains unclear whether factors affecting physical functions remain following TNF therapy. The objective of our study was to assess factors affecting improvement of physical functions and to shed light on relations to disease activity and structural changes in patients with RA treated with etanercept. The study enrolled 208 patients, all of whose composite measures regarding clinical, radiographic, and functional estimation both at 0 and 52 weeks after etanercept therapy were completed. Mean disease duration of 208 patients was 9.6 years, mean Disease Activity Score for 28 joints (DAS28) was 5.4, and mean van der Heijde modified total Sharp score (mTSS) was 94.6. Mean Health Assessment Questionnaire Disability Index (HAQ-DI) improved from 1.4 at 0 weeks to 1.0 at 52 weeks after etanercept therapy, a 31% reduction, which was much less than changes in DAS28 and mTSS. By multivariate analysis, HAQ-DI and mTSS at baseline were significantly correlated HAQ remission. Median HAQ-DI improved in 100 versus 20% of the HAQ-DI $\leq$0.6 versus $\geq$2.0 groups, respectively. The mTSS cutoff point at baseline to obtain HAQ remission was 55.5. During etanercept treatment in the mTSS <55.5 versus >55.5 groups, median HAQ-DI improved in 70 versus 39%; remission was achieved in 59 versus 33%; and there was no improvement in14 versus 30%, respectively. HAQ-DI improvement was significantly correlated with that of DAS28 but not of mTSS. In conclusion, higher HAQ and mTSS at baseline inhibits HAQ-DI improvement within 1 year of etanercept treatment, and the cutoff point necessary for mTSS to improve physical functions in patients with RA was 55.5.

Keywords Rheumatoid arthritis · Anti-TNF · Treatment · Disease activity · Physical function

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes significant morbidity and mortality. Tumor necrosis factor (TNF) plays a pivotal role in the pathological processes of RA through accumulation of inflammatory cells and self-perpetuation of inflammation, leading to joint destruction. The combined use of biologics targeting TNF and methotrexate (MTX) has revolutionized RA treatment, producing significant improvements in clinical, radiographic, and functional outcomes that were not previously observed, as well as producing the emerging outcome of clinical, structural, and functional remission [1–5]. Among them, the most important endpoint is

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improvement and maintenance of physical functions and functional remission, but the relevance of clinical and structural factors affecting physical functions and limiting improvement of physical functions remain unclear.

The safety and efficacy of the representative TNF inhibitor etanercept, a fully human TNF soluble receptor Fc fusion protein, have been reported in patients with active RA regardless of treatment with MTX [6–10]. One of the most important reports regarding long-term safety, maintenance, and efficacy of etanercept for RA was reported by Weinblatt et al. [11–13]. In their studies, the Health Assessment Questionnaire Disability Index (HAQ-DI) score assessing physical functions decreased rapidly, and the HAQ-DI reductions were clinically significant and maintained for >10 years in all RA patients treated with etanercept. Also, greater median reductions in HAQ-DI scores occurred in patients with early (mean duration 1 year) compared with longstanding (mean duration 12 years) RA, and that difference was sustained at each observation point for 10 years, implying that HAQ-DI improvement is limited in longstanding RA patients. Furthermore, HAQ-DI decreased rapidly within 1 year, and the reduction maintained for 10 years and median HAQ-DI responses at year 11 were 0.4 for the early and 0.9 for longstanding RA patients, suggesting that HAQ-DI score at 10 years after initiation of etanercept therapy depends on HAQ-DI changes at during the first year of treatment [11]. Hence, it appears that physical function after a decade of etanercept therapy depends on the degree of HAQ-DI reduction within the first year of treatment initiation.

However, factors affecting reduced physical function at the initial 1 year remain unclear. Based on this background, the multicenter study reported here was undertaken to assess factors at baseline affecting improvement of physical functions, shedding light on not only disease activity but also on structural values to evaluate progression of articular destruction.

Materials and methods

Patients and methods

Data and information on RA patients that fulfilled the diagnostic criteria of the American College of Rheumatology (ACR) [14] were collected from the major rheumatology centers in Japan, including the First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health Japan, Kitakyushu; the Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Saitama; Department of Rheumatology and Clinical Immunology, School of Medicine, Keio University; and the Institute of Rheumatology, Tokyo Women's Medical University. This retrospective study (the ENRICH study) enrolled 208 patients with RA, all of whose information collection regarding composite disease activities, functional ability, and physical functions both at 0 and 52 weeks after initiation of etanercept therapy was completed. All patients who received etanercept treatment (25 mg twice a week in 203 patients and 25 mg once a week in five patients) by March 2009 were registered. The study design was approved by each institution, and informed consent was obtained from each patient before etanercept treatment was undertaken. Demographic data, including disease duration and concomitant therapy, were collected from medical charts. The following parameters were evaluated before and at 52 weeks after the initial etanercept therapy: tender joint count (TJC) 28, swollen joint count (SJC) 28, patient's global assessment of disease activity (PGA), and C-reactive protein (CRP). Disease activity of individual patients was assessed by the Disease Activity Score for 28 joints (DAS28) erythrocyte sedimentation rate (ESR) or DAS28-CRP, calculated according to the authorized formula (http://www.das-score.nl/). Concomitant use of MTX was instituted in all patients, although dose was determined by each attending physician. Joint damage was assessed by van der Heijde modified total Sharp score (mTSS). X-ray images of hands and feet at baseline, study entry, and 1 year after the study were available and evaluable for 120 patients due to loss of radiographs and/or low-quality of X-ray images. Two expert readers independently scored articular damage and progression in a blinded fashion according to the mTSS scoring method. Difference of the two readers' scores for each patient's radiographs was <1% of the maximum mTSS score—that is, 448 [15–17]. Patient demographic indicators and baseline disease characteristics are summarized in Table 1.

Statistical analysis

Patient's baseline characteristics are summarized in Table 1 using the mean values for continuous variables. All multivariate analyses were conducted using the variables of gender, age, disease duration, DAS28-ESR score, DAS28-CRP score, tender joint count (TJC) (0–28), swollen joint count (SJC) (0–28), PGA (0–100 mm, visual analogue scale), ESR, CRP, HAQ-DI, rheumatoid factor (RF), MTX dose, and prednisolone (PSL) dose at baseline. Spearman's correlation analyses were performed to evaluate the association between multivariables at baseline and at 52 weeks after initiation of etanercept therapy (last observation carried forward) of 208 patients. Logistic regression analysis was carried out to estimate HAQ-DI at 52 weeks as dependent variables (probability), and by mTSS at 0 weeks

Table 1 Demographic indicators and baseline disease characteristics

	Mean	Standard deviation	Maximum	Median	Minimum
Age	54.6	13.4	84.0	56.0	18.0
Sex	$f = 83.1\%$				
Duration (year)	9.6	8.2	41.0	8.0	1.0
MTX	w/= 65%				
CS	w/= 68%				
Prior biologics	w/= 20%				
RF	210	346	3510	116	0
MMP-3	278	311	2400	178	8
SJC	7.5	5.2	28.0	6.5	0.0
TJC	7.5	6.3	28.0	6.0	0.0
CRP (mg/dl)	2.9	3.1	23.4	1.9	0.0
ESR (mm/1 h)	51.9	25.6	140.0	49.0	2.3
GH (mm/100 mm)	56	23	100	60	1
DAS28-ESR	5.5	1.1	8.2	5.6	2.9
DAS28-CRP	4.9	1.2	7.8	4.9	2.2
HAQ-DI	1.4	0.8	3.0	1.4	0.0
mTSS	94.6	79.6	378.0	74.0	6.0
EJ	47.9	47.5	233.0	37.5	0.0
JSN	46.7	33.9	145.0	38.6	0.0
ΔmTSS	15.2	16.1	133.8	11.3	0.5

Data are number of patients (%) for categorical data and means for continuous data. Statistical difference was assessed by nonparametric Wilcoxon t test and P (Prob > ChiSq) values are shown. Data supplied for 208 patients with RA

HAQ-DI Health Assessment Questionnaire Disability Index, *DAS28* Disease Activity Score for 28 tender and 28 swollen joints, *CS* corticosteroid, *RF* rheumatoid factor, *MMP-3* matrix metalloprotease-3, *SJC* swollen-joint count, *TJC* tender-joint count, *GH* Global Health Assessment, *CRP* C-reactive protein, ESR erythrocyte sedimentation rate, *EJ* erosive joint, *JSN* joint-space narrowing, *mTSS* van der Heijde modified total Sharp score, Δ estimated yearly progression

as independent variables. A receiver operating characteristic (ROC) curve was developed based on logistic analysis, and the significant cutoff point was determined from the curve. For categorical response parameters, group comparisons were made using a nonparametric Wilcoxon t test. Statistical analyses were performed using JMP software version 8 (SAS Institute, Cary, NC, USA). All reported P values are two sided; $P < 0.05$ was considered significant.

Results

Changes in DAS28, ΔmTSS, and HAQ-DI in patients with RA before and after etanercept treatment

Demographic indicators and baseline characteristics of the 208 patients were: mean age 54.6 years; mean disease duration 9.6 years; mean HAQ-DI 1.4; mean DAS28-ESR 5.5, implying that most patients had highly active disease; and mean mTSS 94.6, indicating that the population included patients with long-established RA (Table 1). Mean DAS28-CRP was 4.9 at baseline, but DAS28-CRP at 52 weeks after initiation of etanercept treatment was 2.6 ($P < 0.0001$ by nonparametric Wilcoxon t test), producing a 46% reduction in DAS (Fig. 1a). Furthermore, as shown in the probability plot, score improvement was observed in the majority of patients, and 55% reached DAS remission, showing values of DAS28 < 2.6 (Fig. 1d). Estimated yearly mTSS progression (ΔmTSS) at 0 weeks was 15.3, whereas that at 52 weeks after etanercept therapy was 2.0 ($P < 0.0001$ by nonparametric Wilcoxon t test), producing a 87% reduction rate in joint destruction (Fig. 1b). In addition, progression was completely inhibited in 48% of patients (Fig. 1e). In contrast, after initiation of etanercept treatment, the HAQ-DI at 52 weeks was not markedly improved, and patients who showed higher HAQ-DI appeared to remain unchanged (Fig. 1c), although the mean HAQ-DI improved from 1.4 at 0 weeks to 1.0 at 52 weeks. The reduction in HAQ-DI from 0 to 52 weeks was 31%, which was much less than changes of DAS28-CRP and ΔmTSS; a similar probability curve was observed before and after initiation of etanercept treatment (Fig. 1f).

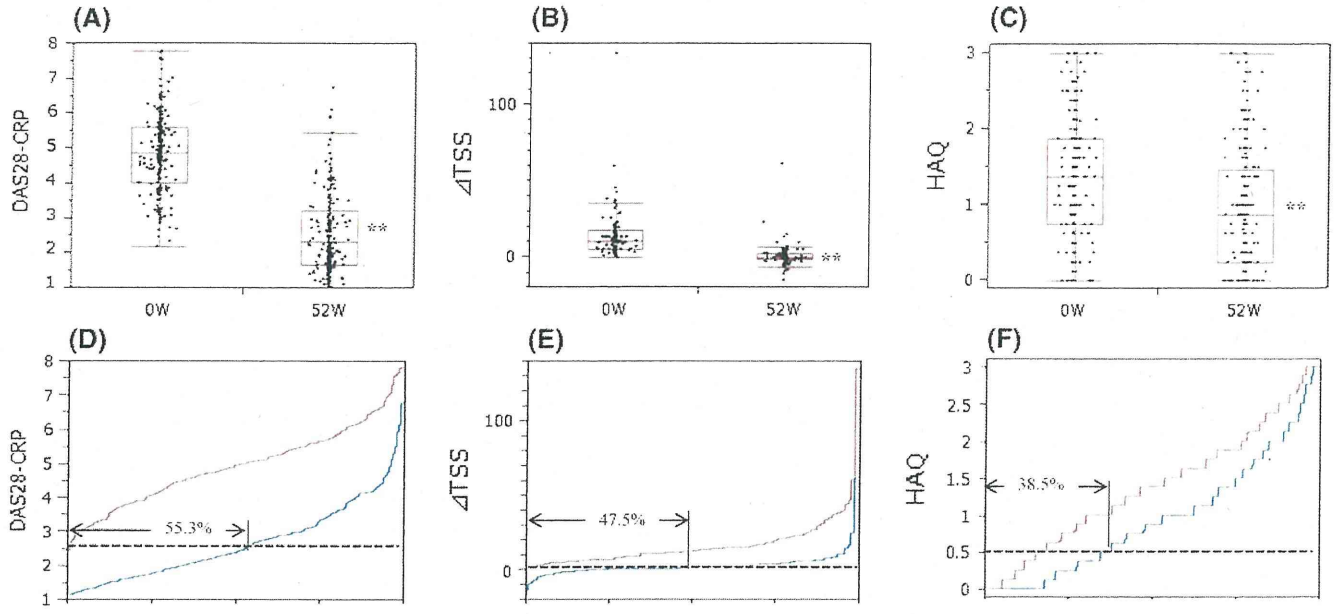

Fig. 1 Disease Activity Score for 28 joints (DAS28) values (**a**, **d**), yearly progression of modified total Sharp score (mTSS) (**b**, **e**), and Health Assessment Questionnaire Disability Index (HAQ-DI) values (**c**, **f**) in patients with rheumatoid arthritis (RA) at 0 and 54 weeks after the start of etanercept therapy. *Upper panels* show distribution of values, mean ± standard deviation (SD), and median, with the 25th and 75th percentiles of DAS28 values (**a**), yearly mTSS progression (**b**), and HAQ (**c**) at 0 and 52 weeks after initiation of etanercept treatment. *Lower panels* are probability plots of DAS28 values (**d**), yearly progression of mTSS (**e**), and HAQ values (**f**) at 0 (*red lines*) and 54 (*blue lines*) weeks after initiation of etanercept treatment. Statistical difference was assessed by nonparametric Wilcoxon t test (*$P < 0.05$, **$P < 0.01$)

Effects of HAQ-DI at baseline on HAQ-DI improvement in RA patients treated with etanercept

To clarify background factors related to HAQ-DI improvement with etanercept therapy, we assessed the relationship between achievement of HAQ-remission (<0.5) at 52 weeks of the treatment and a series of clinical parameters at baseline using multivariate analysis after adjusting for confounding variables. Although no significant correlations between HAQ remission at 52 weeks and the majority of a series of clinical parameters were found, HAQ-DI ($P < 0.0001$) and mTSS ($P = 0.0138$) at baseline were significantly correlated with HAQ remission after initiation of etanercept therapy (Table 2).

Subsequently, changes in HAQ-DI were estimated in patients groups divided by upper quartile (HAQ-DI $\geq$ 2.0), lower quartile (HAQ-DI $\leq$ 0.6), and median values (0.6 < HAQ-DI < 2.0) at the baseline. Mean HAQ-DI at 0 weeks was 2.5 and median was 2.5 at baseline in patients in the upper quartile. Median HAQ-DI was changed from 2.5 to 2.0, producing only a 20% improvement in the upper group (Fig. 2a). Conversely, mean HAQ-DI improved from 0.3 at 0 weeks to 0.2 at 52 weeks and median HAQ-DI from 0.3 to 0, indicating a 100% improvement in median HAQ-DI in the lower-quartile group at baseline (Fig. 2c). We further assessed changes in HAQ-DI based on the difference of HAQ-DI values and mTSS value at baseline. The HAQ-DI significantly and similarly decreased in patients whose baseline HAQ-DI was $\geq$ 2.0 and >73.0, the upper half of mTSS values (Fig. 3a); or HAQ-DI $\geq$ 2.0 and mTSS < 73.0 (Fig. 3d).

Effects of mTSS at baseline on HAQ-DI improvement in RA patients treated with etanercept

Next, logistic regression analysis to estimate the probability of HAQ-DI $\leq$ 0.5 at 52 weeks after initiation of etanercept therapy as a dependent variable and by mTSS at 0 weeks as independent variable was performed. A significant logistic regression curve was drawn between the dependent and independent variables ($P < 0.001$). From the ROC curve based on the analysis, the cutoff point of mTSS at baseline was 55.5 to achieve HAQ remission. Subsequently, one-way analysis of HAQ-DI at week 52 by mTSS at 0 weeks for <55.5 versus >55.5 was performed. Mean HAQ-DI at 0 weeks was 1.6 at baseline in patient group mTSS > 55.5 at 0 weeks. The median HAQ-DI changed from 1.9 to 1.1, producing a 39% improvement of HAQ-DI in the mTSS > 55.5 patient group (Fig. 4a). Conversely, median HAQ-DI improved from 1.3 at 0 weeks to 0.4 at 52 weeks, indicating a 70% improvement of median HAQ-DI in patient group mTSS < 55.5 at

Table 2 Multivariant logistic analysis affecting Health Assessment Questionnaire (HAQ) at week 52 after initiation of etanercept treatment

	Estimated value	Standard error	*t* value	*P* value (Prob > |*t*|)
Duration	0.0050	0.0092	0.55	0.5817
MTX dose	−0.0243	0.0129	−1.88	0.0639
Corticosteroid	0.2099	0.1199	1.75	0.0840
RF	0.0000	0.0002	0.31	0.7571
DAS28-CRP	−0.0519	0.0722	−0.72	0.4748
ESR	0.0020	0.0026	0.76	0.4518
CRP	−0.0155	0.0322	−0.48	0.6309
HAQ	0.6472	0.0853	7.59	<0.0001*
mTSS	0.0025	0.0009	2.52	0.0138*

MTX methotrexate, *RF* rheumatoid factor, *DAS28-CRP* Disease Activity score for 28 joints C-reactive protein; *ESR* erythrocyte sedimentation rate, *HAQ* Health Assessment Questionnaire, *mTSS* modified total Sharp score

* *P* values <0.05 were considered significant. Data supplied for 208 patients with RA

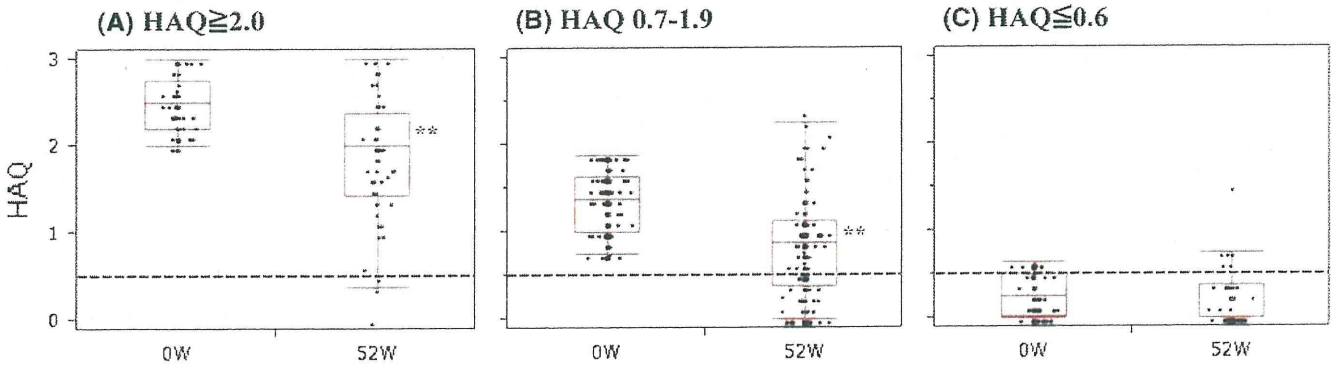

Fig. 2 Changes in Health Assessment Questionnaire (HAQ) values divided by baseline HAQ values before and after treatment with etanercept. One-way analysis of HAQ at 52 weeks after treatment by HAQ at 0 weeks, >2.0;upper 25th percentile of HAQ values (**a**); <0.6, lower 25th percentile (**c**); and between 0.7 and 1.9 between the 25th and 75th percentile (**b**) was performed. Statistical difference between the two groups was determined by nonparametric Wilcoxon *t* test (*$P < 0.05$, **$P < 0.01$)

baseline. HAQ remission was observed in 59% of patients whose mTSS was <55.5 at 0 weeks, whereas only 33% of the mTSS > 55.5 group at 0 weeks reached HAQ remission after therapy (Fig. 4a, b).

Median $\Delta HAQ_{[0-52\ weeks]}$ of patients whose mTSS was <55.5 and >55.5 at baseline was −0.63 and −0.38, respectively; and 14 versus 30% of patients with mTSS < 55.5 and >55.5, respectively; revealed no improvement in HAQ-DI following etanercept therapy (Fig. 3c, d). Furthermore, $\Delta HAQ_{[0-52\ weeks]}$ was significantly correlated with $\Delta DAS28_{[0-52\ weeks]}$ ($r = -0.029$, $P < 0.0001$), whereas no correlation was found between $\Delta HAQ_{[0-52\ weeks]}$ and $\Delta mTSS_{[0-52\ weeks]}$ ($r = -0.527$, $P = 0.427$) during etanercept therapy (Fig. 5). These results indicate that higher mTSS at baseline appears to inhibit improvement in HAQ-DI and that improvement in DAS28 but not mTSS affects improvement in HAQ-DI in patients with RA treated with etanercept within the 1 year.

Discussion

The combined use of TNF inhibitors and MTX has produced significant improvements in clinical, radiographic, and functional outcomes that were not previously seen and has revolutionized the treatment goal of RA to clinical, structural, and functional remission [1–5]. In the study population reported here, whose mean disease duration was 9.6 years and mean DAS28-ESR was 5.5, 55% reached clinical remission and 48% achieved structural remission at 52 weeks after initiation of etanercept treatment. However, the HAQ-DI, a marker of physical function, at 52 weeks was not markedly improved, and patients who showed higher HAQ-DI appeared to remain unchanged by etanercept therapy. Probability plot analysis also showed inferior improvement in HAQ-DI than that in DAS28, a marker of clinical disease activity; and ΔmTSS, a marker of radiographic change; and probability curve of HAQ-DI was

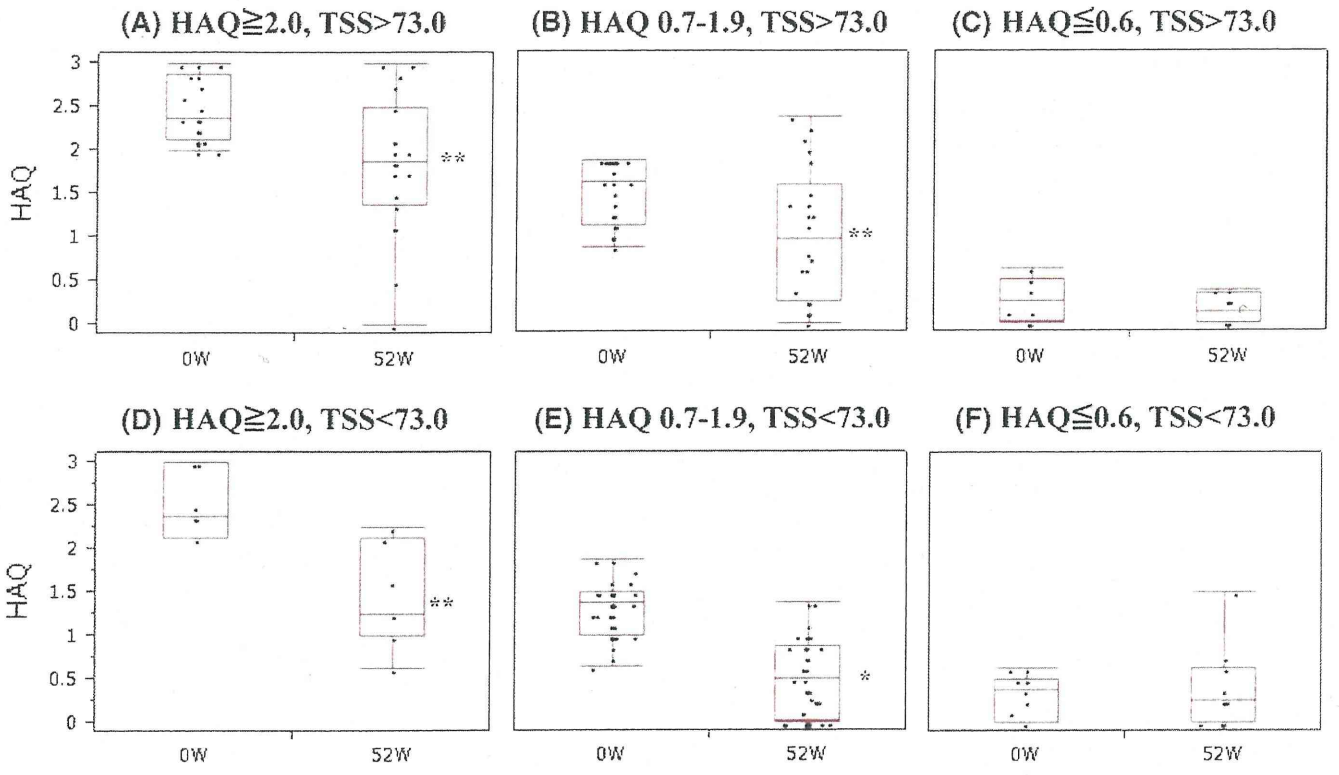

Fig. 3 Changes in Health Assessment Questionnaire (HAQ) values divided by baseline HAQ values and modified total Sharp score (mTSS) values before and after etanercept treatment; one-way analysis of HAQ at 52 weeks after treatment, at 0 weeks, >2.0; upper 25th percentile of HAQ values and >73.0; upper half of mTSS values (**a**) or <73.0; lower half or mTSS (**d**) <0.6; lower 25th percentile of HAQ and mTSS > 73.0 (**c**), or mTSS < 73.0 (**f**), and between 0.7 and 1.9 between the 25th and 75th percentile of HAQ and mTSS > 73.0 (**b**) or mTSS < 7.3 (**e**). Statistical difference of the two groups was determined by nonparametric Wilcoxon *t* test (*$P < 0.05$, **$P < 0.01$)

similar before and after etanercept therapy. Accordingly, we assessed the background factor affecting HAQ-DI improvement using multivariate analysis and found that HAQ-DI and mTSS at baseline were significantly correlated with HAQ remission after the etanercept therapy. Actually, median HAQ-DI improved within 1 year from 2.5 to 2.0, producing only a 20% improvement, in patients whose HAQ-DI at baseline was categorized at the upper quartile (HAQ-DI $\geq$ 2.0). Median HAQ-DI improved from 0.3 to 0, producing a 100% improvement in patients whose HAQ-DI at baseline was in the lower quartile (HAQ-DI $\leq$ 0.6). Thus, higher HAQ at baseline appears to inhibit HAQ-DI improvement with etanercept therapy.

Another important background factor affecting HAQ-DI improvement with the etanercept therapy was mTSS at baseline. The ROC curve based on logistic regression analysis and the cutoff point of mTSS at baseline was determined to be 55.5 for the probability of HAQ-DI $\leq$ 0.5 at 52 weeks after the therapy. Actually, within 1 year, median HAQ-DI improved from 1.9 to 1.1, a 39% improvement, in patients whose mTSS was >55.5 at baseline. Median HAQ-DI improved from 1.3 to 0.4, a 70% improvement of median HAQ-DI, in patients whose mTSS was <55.5 at baseline; also, HAQ remission was observed in 33 and 59% of patients, respectively at 0 weeks. HAQ-DI was not improved by etanercept therapy in 30 and 14% of patients whose mTSS was >55.5 and <55.5 at the baseline, respectively. Furthermore, although improvement in HAQ was significantly correlated with that of DAS28 within a year of etanercept therapy initiation, it was not related to changes in mTSS. From these results, higher mTSS (>55.5) at baseline appears to interfere with HAQ-DI improvement, implying that functional improvement cannot be easily obtained in patients whose mTSS is >55.5. Although this explanation may be too simple, it seems that calculations using our data indicate that the mean ΔmTSS of our study population at baseline was 15.2 and that mTSS could reach 55.5 within 4 years. Physical function, thereby, cannot improve unless patients are treated with MTX and TNF inhibitors within 4 years of disease onset. Therefore the first 4 years may be a "window of opportunity" to prevent disease progression to functional disability.

Impaired physical function in patients with RA is governed by various factors, but Smolen et al. [18, 19] reported

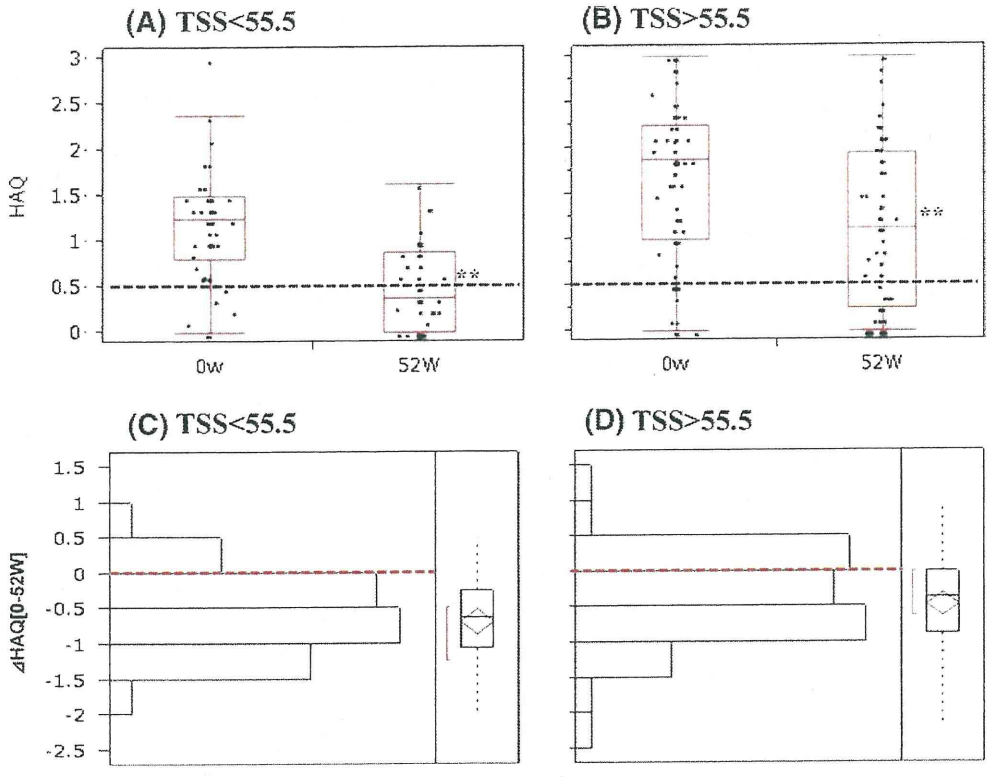

Fig. 4 Changes of Health Assessment Questionnaire (HAQ) values, divided by baseline modified total Sharp score (mTSS) values before and after initiation of etanercept treatment. From receiver operating characteristic (ROC) curve based on logistic regression analysis, the cutoff point of mTSS before treatment was 55.5. Subsequently, one-way analysis of HAQ at 0 and 52 weeks after treatment according to mTSS <55.5 group at baseline (**a**) and >55.5 group at baseline (**b**) was performed, and the statistical difference of the two groups was sought by nonparametric Wilcoxon *t* test (*$P < 0.05$, **$P < 0.01$). Histogram of estimated yearly progression in Health Assessment Questionnaire ($\Delta HAQ)_{[0-52\ weeks]}$, distribution of values, mean ± standard deviation (SD), and median, with the 25th and 75th percentiles of the values divided by mTSS at baseline for the <55.5 (**c**) and >55.5 (**d**) groups are shown

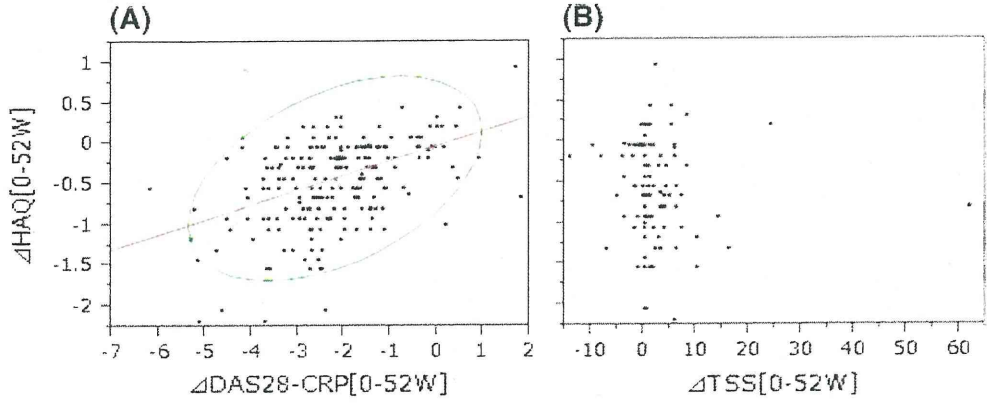

Fig. 5 Correlation between estimated yearly progression in Health Assessment Questionnaire Disease Index (ΔHAQ-DI) and Disease activity Score for 28 joints (ΔDAS28) (**a**) and between ΔHAQ-DI and modified total Sharp score (ΔmTSS) (**b**). *Dot plot* represents an individual value, and the *circle* represents the 95% confidence interval (95% CI). Correlation between $\Delta HAQ_{[0-52\ weeks]}$ and $\Delta DAS28_{[0-52\ weeks]}$ (**a**) and between $\Delta HAQ_{[0-52\ weeks]}$ and $\Delta mTSS_{[0-52\ weeks]}$ (**b**) during etanercept therapy

that HAQ is composed of disease-activity-related HAQ and damage-related HAQ; changes in activity HAQ were mainly due to changes in disease activity, although there was little damage during a short-term therapeutic intervention, whereas HAQ would worsen with increasing damage. Actually, HAQ-DI similarly decreased in a group of patients whose baseline mTSS was >73.0 and in another group with mTSS <73.0, indicating that HAQ

improvement did not depend on baseline mTSS and that etanercept improved activity-related HAQ. Those authors also reported that for every 10 mTSS units, HAQ increase by 1/10th of a unit. Their description is similar to results of our study, in which the cutoff point of mTSS at baseline was 55.5 and a critical HAQ-DI was 0.6 in order to obtain significant improvement or functional remission of HAQ-DI with etanercept therapy. Furthermore, as a recent report indicated that physical disability in RA was associated with cartilage damage rather than bone erosion, further analysis regarding the relevance of joint-space narrowing or bone erosion to changes in HAQ-DI are warranted [20]. Beyond these points, mTSS $>$ 55.5 and/or HAQ-DI $\geq$ 0.6, HAQ-DI would be highly indicative of damage-related HAQ, and these may be critical levels at which structural damage becomes irreversible, even with etanercept and MTX treatment.

We analyzed the relationship between absolute values and changes in DAS28, mTSS, and HAQ-DI simultaneously and found that physical functions cannot improve if joint destruction has progressed beyond the critical level of mTSS $>$ 55.5. Thus, appropriate intervention using TNF inhibitors is strongly recommended during the window of opportunity, when RA patients are treated by addressing the upcoming endpoint for treatment: improvement and maintenance of physical functions.

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Conflict of interest Y. Tanaka has received consulting fees, speaking fees, and/or honoraria from Mitsubishi-Tanabe, Chugai, Eisai, Takeda, Astellas, and Abbott and has received research grant support from Mitsubishi-Tanabe, Takeda, MSD, Pfizer, Astellas, Chugai, Abbott, and Eisai. H Yamanaka has received Research grant from Chugai Pharmaceutical, Astellas Pharma Inc., Wyeth K. K., Daiichi Sankyo, Banyu Pharmaceutical, Mitsubishi Tanabe Pharma, Abbott Japan, Eisai, Santen Pharmaceutical, Taishotoyama Pharmaceutical, Takeda Pharmaceutical Company Limited, Kissei Pharmaceutical, Janssen Pharmaceutical K.K. and lecture fee and/or consulting fee from Abbott, Eisai, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Janssen Pharmaceutical, Hoffmann-La Roche, Chugai Pharmaceutical, Pfizer. S Momohara has received speaking fees from Mitsubishi Tanabe Pharma Corporationfrom, Abbott Japan Co., Ltd., and Santen Pharmaceutical Co., Ltd. H. Kameda has received honoraria from Abbott, Centocor Ortho Biotech, Chugai Pharma, Eisai Pharmaceuticals, Mitsubishi Tanabe Pharma, Takeda Pharmaceuticals, Wyeth Japan. K. Amano has received honoraria from Abbott, Chugai Pharmaceutical, Eisai Pharmaceuticals, Mitsubishi Tanabe Pharma, Takeda Pharmaceuticals, Wyeth Japan. T. Takeuchi has received honoraria from the following companies: Abbott, Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai Pharmaceuticals, Janssen Pharmaceutica, Mitsubishi Tanabe Pharma, Novartis, Takeda Pharmaceuticals, Wyeth Japan.

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Original article

Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients—REACTION 52-week study

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Abstract

Objectives. To evaluate the effectiveness and safety of tocilizumab in RA patients in clinical practice.

Methods. We observed 232 consecutive RA patients who began tocilizumab in three rheumatology centres in Japan for 52 weeks. Clinical, radiographic and functional status and safety were evaluated.

Results. Mean age of the 232 patients was 59.1 years, mean duration of disease was 12.4 years and average DAS using the 28-joint count (DAS-28) was 5.6. Although 62.8% of the patients had been treated previously with anti-TNF biologics, clinical remission at Week 52 was achieved in 43.7%, radiographic non-progression in 62.8% and functional remission in 26.4%. Retention rate at Week 52 was 71.1%, and the same for those with or without previous anti-TNF treatment. Adverse drug reactions leading to tocilizumab discontinuation were observed in 15.5% of patients, the most frequent adverse drug reaction being pneumonia in eight cases. On multivariate logistic regression analysis, DAS-28, HAQ-disability index (HAQ-DI), concomitant MTX and concomitant glucocorticoids (GCs) were predictive variables for clinical remission at Week 52 of tocilizumab treatment. In particular, HAQ-DI was found to be a predictive variable for remission of all three types—clinical, radiographic and functional—at Week 52 of tocilizumab treatment.

Conclusions. In daily clinical practice, tocilizumab exhibited excellent effectiveness in established RA patients, some of whom had failed to respond to previous anti-TNF treatment. Although further detailed safety findings are required, this study provides valuable real-world findings on the management of RA with tocilizumab.

Key words: Rheumatoid arthritis, Tocilizumab, Remission, Joint destruction, Health assessment questionnaire.

SCIENCE

Introduction

Pro-inflammatory cytokines play a fundamental role in the inflammatory processes leading to destructive arthritis in patients with RA [1, 2]. Biological agents against pro-inflammatory cytokines such as TNF-α have dramatically changed the management of patients with RA [1, 2]. It is now recommended to treat RA patients to achieve clinical remission by early and tight control of disease activity with intensive medication [3, 4]. Recent clinical trials have shown that treatment with anti-TNF biologics in combination with MTX in early RA can lead to clinical remission in ~50% of patients [5]; however, the remaining half of the patients are either those not able to achieve clinical

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remission or discontinued anti-TNF biologics and switched to other medications [6–8]. A new biological agent, tocilizumab, targeting the IL-6 receptor has recently been approved for use in patients with RA in more than 40 countries around the world, including Japan, drawing attention to the effectiveness and safety of tocilizumab in clinical practice [9–11]. Generally, randomized clinical trials (RCTs) are considered the gold standard for evaluation of the efficacy of newly developed agents. However, RCTs are artificial and may not reflect efficacy and safety in the real rheumatology world.

While we have reported the effectiveness of tocilizumab at Week 24 [12], there is no report that evaluates all efficacy with regard to clinical remission, structural remission and functional remission of tocilizumab comprehensively under daily clinical practice. Hence we undertook the Retrospective Actemra Investigation for Optimal Needs of RA Patients (REACTION 52-week study) to confirm the efficacy and safety of tocilizumab in daily clinical practice.

Patients and methods

Patients

All RA patients included in this study fulfilled the ACR classification criteria [13]. After the approval of tocilizumab in April 2008 in Japan, all patients from three rheumatology centres in Japan (the Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Saitama; the First Department of Internal Medicine, School of Medicine, University of Occupational & Environmental Health Japan, Kitakyushu; and the Institute of Rheumatology, Tokyo Women's Medical University) who had started to receive tocilizumab by March 2009 were consecutively registered into this study and were followed up every 4 weeks at the time of infusion. We analysed a total of 232 RA patients who had been observed for 52 weeks from the initial infusion of tocilizumab.

The REACTION study was a retrospective observational study using anonymized information, and conformed to standard tocilizumab treatment proposed by the Japan College of Rheumatology (JCR). Patients' written consent was obtained according to the Declaration of Helsinki.

Tocilizumab treatment and assessment of effectiveness

Tocilizumab was infused every 4 weeks at a dose of 8 mg/kg according to the drug labelling and the tocilizumab therapy guidelines of the JCR [14]. In the JCR guidelines, tocilizumab is recommended for patients who show an inadequate response despite treatment for at least 3 months with the maximum permissible dose of one of the non-biologic DMARDs. Demographic data, including disease duration and concomitant therapy, were collected from the medical charts. The following parameters were evaluated every 4 weeks for 52 weeks following the initial infusion of tocilizumab: tender joint count (TJC) 28, swollen joint count (SJC) 28, patient's global assessment (Pt-GA) of disease activity, physician's global assessment (Ph-GA) of disease activity, ESR, CRP, MMP-3 and HAQ-disability index (HAQ-DI). Disease activity was assessed by the DAS-28 that was calculated according to the authorized formula [15]. Although there were no criteria for measuring CRP, ESR and MMP-3 in this study protocol, these items are approved for monthly monitoring in RA by the Japanese health insurance system. Eventually, ESR, CRP and MMP-3 were performed at each visit in three institutions as routine clinical practice for all patients treated with tocilizumab.

Among the 232 patients in this study, X-ray images of both the hands and feet at 0 and 52 weeks or last observation were available for 149 patients for assessing radiographic damage. The images were read by two independent, well-trained rheumatologists according to the previously reported van der Heijde-modified Sharp (vdH-Sharp) method [16, 17]. Estimated yearly progression was calculated as previously reported [17, 18]. The last observation carried forward (LOCF) method was used in each analysis and radiographic data were extrapolated to 52 weeks. Clinical remission was defined as a DAS-28 of <2.6, structural remission was defined as a change in total vdH-Sharp score of $\leqslant 0.5$ from baseline to Week 52, and functional remission was defined as HAQ-DI of $\leqslant 0.5$, as previously reported [17].

Statistical analysis

The LOCF method was used in each analysis. Baseline variables of RA patients were analysed for association with clinical, structural and functional remissions at Week 52 using Pearson's chi-square test (for categorical variables) and Student's *t*-test (for continuous variables). Univariate logistic analysis was used to screen for potential predictive variables, and a stepwise selection process was used to generate a multivariate regression model for predicting remission at Week 52 of tocilizumab treatment. All statistical analyses were performed with JMP version 8.0.2 statistical software (SAS Institute Inc., Cary, NC, USA).

Results

Demographic data of patients from three institutions

Baseline characteristics of the 232 patients enrolled in this study are shown in Table 1. Mean age was 59.1 years and mean duration of the disease was 12.4 years, indicating that the RA patients in this study were established and advanced. Disease activity was high, as shown by the mean DAS-28 of 5.6 and mean CRP level of 3.1 mg/dl. Notably, MTX and glucocorticoids (GCs) were concomitantly used in 56 and 66% of the patients, respectively, and 62.8% of the patients had previously experienced treatment with anti-TNF biologics.

Changes in DAS-28 and HAQ-DI during 52 weeks of tocilizumab treatment

As shown in Fig. 1, the DAS-28 score significantly decreased from 5.6 (1.3) at baseline to 4.4 (1.5) at Week 4, 3.8 (1.7) at Week 12, 3.3 (1.6) at Week 24 and 3.2 (1.7)

TABLE 1 Demographic and clinical features of the RA patients (n = 232)

Clinical parameters	Mean (S.D.)	Median (interquartile range)
Age	59.1 (13.3)	61.0 (53.0–68.0)
Gender, female, %	84.3	
Duration, years	12.4 (11.1)	10.0 (4.0–18.0)
Steinbrocker's stages I/II/III/IV, %	7.2/30.5/17.0/45.3	
Steinbrocker's class 1/2/3/4, %	5.0/72.2/22.4/0	
DAS-28	5.6 (1.3)	5.6 (4.9–6.6)
SJC (0–28)	7.7 (5.6)	7 (3–11)
TJC (0–28)	7.9 (6.4)	6 (3–12)
ESR, mm/h	63 (29)	64 (44–85)
CRP, mg/dl	3.1 (2.9)	2.5 (0.9–4.6)
Pt-GA (VAS/100 mm)	56 (24)	54 (40–76)
Concomitant MTX, %	55.6	
Dose of MTX, mg/week	8.6 (3.1)	8.0 (6.0–10.0)
Concomitant GCs, %	66.4	
Dose of GCs, mg/day	5.2 (3.1)	5.0 (3.0–6.0)
Previous anti-TNFs, %	62.8	

at Week 52 ($P < 0.0001$). Disease activity status changed significantly from high disease activity at baseline to clinical remission or low disease activity during treatment with tocilizumab ($P < 0.0001$). Clinical remission was obtained in 14.8% of the patients at Week 4, 27.7% at Week 12, 39.2% at Week 24 and 43.7% at Week 52, indicating that clinical remission was achieved for ~44% of patients and that the rate nearly plateaued at Week 24 in this patient population. Notably, only 14% of the patients showed no response at Weeks 24 and 52. In addition, clinical remission, even when assessed by non-responder imputation methods, was 12.1, 23.3, 34.1 and 39.7% at Weeks 4, 12, 24 and 52, respectively, showing ~3–4% lower than that obtained by the LOCF method. Significant improvements in clinical parameters were observed and the percentage reduction for each parameter at Week 52 compared with at baseline was 63.8% for SJC, 60.5% for TJC, 33.7% for Pt-GA, 70.4% for ESR, 82.6% for CRP and 56.0% for MMP-3.

HAQ-DI similarly decreased significantly from 1.56 (0.80) at baseline to 1.29 (0.87) at Week 52 ($P = 0.0009$). However, improvement in HAQ-DI compared with baseline score (change in HAQ-DI $\geqslant 0.22$) was observed in only 45.6% of patients at Week 52. Although functional remission (HAQ-DI $\leqslant 0.5$) increased significantly from 12.4% at baseline to 26.4% at Week 52, categorical analysis of HAQ-DI did not show any statistical change ($P = 0.1352$).

Effects of medication on clinical and functional response

As shown in Fig. 2, DAS-28 at Week 52 was significantly lower in patients receiving concomitant MTX than in those not receiving it [2.92 (1.46) and 3.45 (1.82), respectively; $P = 0.0336$]. HAQ-DI was also significantly lower in those receiving MTX than in those not receiving it [1.12 (0.83) *vs* 1.55 (0.85); $P = 0.0005$]. In contrast, DAS-28 at Week 52 was significantly higher in patients receiving concomitant GCs than in those not receiving them [3.34 (1.58) *vs* 2.87 (1.79); $P = 0.0037$]. Again, HAQ-DI at Week 52 was also higher in patients receiving GCs than in those not receiving them [1.40 (0.88) *vs* 1.07 (0.82); $P = 0.0071$). However, there was no significant difference in either DAS-28 or HAQ-DI at Week 52 between patients who had or had not received previous treatment with anti-TNF biologics.

Inhibition of radiographic damage by tocilizumab treatment

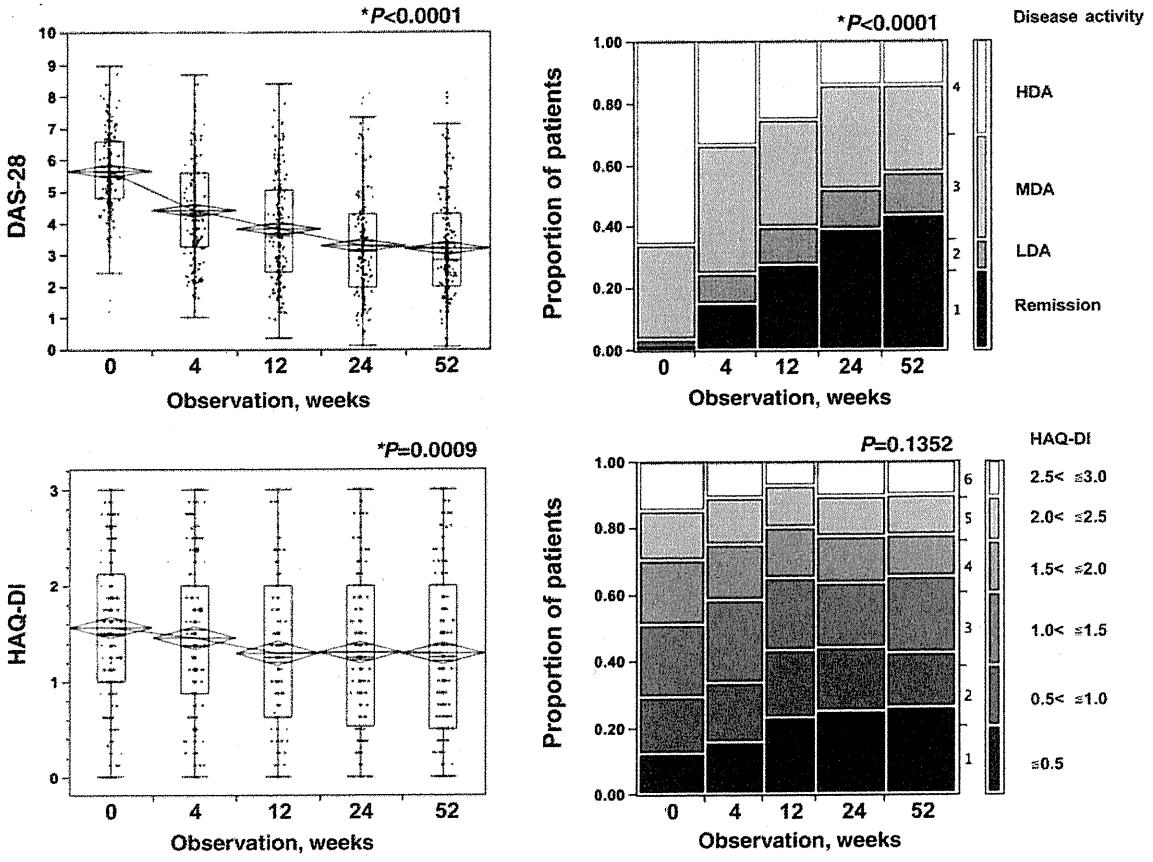
Radiographic damage was evaluated in 149 of the 232 patients. Most baseline parameters as well as clinical and functional response at Week 52 did not differ significantly between the patients who underwent radiographic evaluation ($n = 149$) and those who did not ($n = 83$) (data not shown).

There was no significant difference between total vdH–Sharp score at Week 0 and that after 52 weeks of tocilizumab treatment [140.5 (101.2) *vs* 142.1 (101.3); $P = 0.8916$], and erosion score and joint space narrowing (JSN) score were similarly not significantly changed. The mean change from Week 0 to 52 of tocilizumab treatment was 1.07 (2.87) for total vdH–Sharp score, 0.50 (1.34) for erosion score and 0.58 (1.95) for JSN score, which appears to be clinically sufficient for tocilizumab to inhibit structural damage. As judged by a change in total vdH–Sharp score of $\leqslant 0.5$, 62.8% of the patients showed no radiographic progression (Fig. 3a). For the structural damage, treatment with tocilizumab greatly reduced the estimated yearly progression of the total vdH–Sharp score from 20.8 (22.9) at baseline to 1.1 (2.9) (Fig. 3b). There were no differences in the effect of structural damage among patients with different durations of disease. Interestingly, progression of joint destruction was similar with or without concomitant MTX, GCs or previous use of anti-TNF biologics. Each estimated yearly progression by RA patients treated with or without anti-TNF biologics was dramatically decreased from 18.3 (19.3) at baseline to 0.9 (2.4) at 52 weeks (96% reduction) and 24.8 (27.4) at baseline to 1.4 (3.5) at 52 weeks (94% reduction), respectively.

Retention rate during 52 weeks of treatment with tocilizumab

The retention rate of this study was 92.0% at Week 12, 83.0% at Week 24 and 71.1% at Week 52. Sixty-seven (28.9%) patients discontinued tocilizumab treatment because of adverse events (AEs) (38/67, 56.7%), lack of efficacy (21/67, 31.3%), remission (1/67, 1.5%) and other reasons (7/67, 10.4%). Retention rate was higher for patients with concomitant MTX than for those without it (77.1 *vs* 66.0%), and was lower for those with concomitant GCs than those without (68.7 *vs* 78.4%), while it did not differ between those with or without previous treatment with anti-TNF biologics (72.5 *vs* 70.9%).

FIG. 1 Change in DAS-28 and HAQ-DI scores over 52 weeks of tocilizumab treatment. Upper panels show the change in DAS-28 [left: distribution of the values, mean (S.D.), and median with first and third quartile points of DAS-28; right: categorical distribution of disease activity status]. Lower panels show the change in HAQ-DI [left: distribution of the values, mean (S.D.), and median with first and third quartile points of HAQ-DI; right: categorical distribution of disability status]. HDA: high disease activity; MDA: moderate disease activity; LDA: low disease activity.



Baseline variables predictive of clinical, structural and functional remission at Week 52

Since there are substantial confounding factors contributing to the clinical, radiological and functional responses to tocilizumab treatment, we next searched for independent predictive baseline parameters for clinical, structural and functional remission at Week 52. Based on the results of a univariate logistic regression analysis, age, disease duration, DAS-28, HAQ-DI, dose of MTX and dose of GCs at baseline were selected as significant variables for clinical remission at Week 52; estimated yearly progression of total vdH-Sharp score, HAQ-DI and dose of GCs at baseline were selected as significant variables for structural remission at Week 52; and age, disease duration, DAS-28, total vdH-Sharp score, HAQ-DI and dose of MTX at baseline were selected as significant variables for functional remission at Week 52 (Table 2). Multiple regression analysis showed that DAS-28, HAQ-DI, dose of MTX and dose of GCs at baseline were identified as independent predictive variables for clinical remission at Week 52. Yearly progression of total vdH-Sharp score and dose of GCs were found to be the independent predictive variables for structural remission at Week 52: in addition, although HAQ-DI was not a statistically significant predictive variable, it gave an adjusted odds ratio of 0.624 (Table 3). Finally, baseline HAQ-DI was identified as an independent predictive variable for functional remission at Week 52, with an adjusted odds ratio of 0.582.

Safety

In total, 133 AEs and 26 serious AEs (SAEs) were observed in 58 (25.0%) and 26 (11.2%) of 232 patients, respectively. Most of the AEs were infections and laboratory tests. In the category of SAEs, serious infections were reported in 10 (4.3%) patients, and the most common serious infection was pneumonia (4 points, 1.7%). Skin infection and oesophageal candidiasis were also reported in one patient each as SAEs necessitating discontinuation of tocilizumab treatment. In addition, there were two cases each of cerebral bleeding, malignancy (breast and cervix), liver dysfunction, skin eruption and exacerbation

FIG. 2 DAS-28 and HAQ-DI at Week 52 of tocilizumab treatment in RA patients with or without (**a**) concomitant MTX; (**b**) GCs; (**c**) previous treatment with anti-TNF biologics. Distribution of the values, mean (S.D.) and median with first and third quartile points of each clinical parameter are shown.

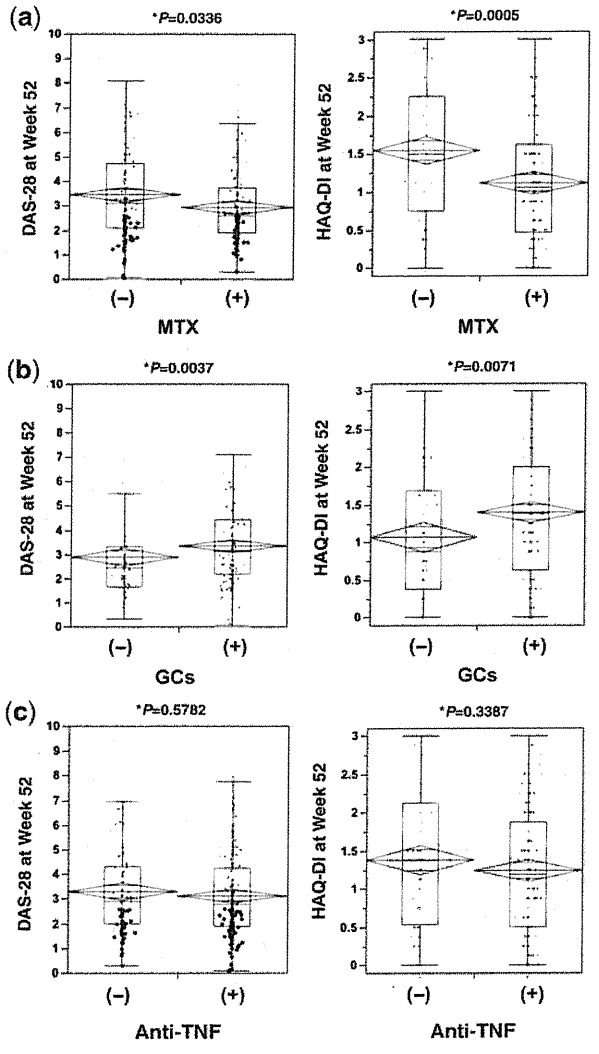
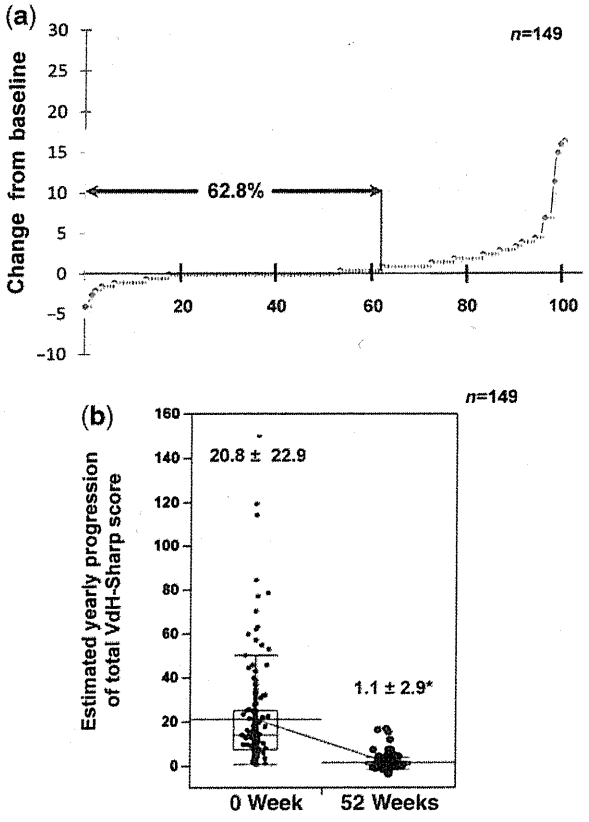


FIG. 3 Effects of radiographic damage before and 52 weeks after tocilizumab treatment by (**a**) the cumulative probability in total vdH-Sharp score and (**b**) estimated yearly progression of total vdH-Sharp score.



of scleroderma, and one case each of acute respiratory failure, myocardial infarction, chest pain, necrotizing pancreatitis and skin ulcer. Gastrointestinal bleeding, gastrointestinal perforation and anaphylaxis were also observed in one patient, leading to discontinuation of further tocilizumab treatment. The most common laboratory abnormalities were increases in lipids, including total, low- and high-density lipoprotein cholesterol in 5 (2.2%) of 232 patients and liver function abnormality, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation in 7 (3.0%) patients. The elevation of serum bilirubin and cytopenia (white blood cells and platelets decreasing) were also reported in two patients each, leading to discontinuation of tocilizumab treatment.

Discussion

In this study, ~44% of patients with established RA and high disease activity achieved clinical remission at Week 52 of tocilizumab treatment, and radiographic non-progression was observed in >60% of patients. Although it is difficult to compare these results with those of other biologics because the patient background factors in each study differed, the efficacy of tocilizumab might be equivalent to or superior to anti-TNF agents compared with a similar type of study, whose DAS-28-CRP remission rate at Week 52 was 27.6% [19].

The Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody (CHARISMA) study [20] suggests that tocilizumab in combination with MTX may be superior to tocilizumab monotherapy, suggesting in turn that the rate of clinical remission with tocilizumab plus MTX combination therapy may also be higher as well. The present study clearly showed that clinical and functional remission rates at 52 weeks were significantly higher for RA patients receiving MTX than those without MTX, whereas in marked contrast, remission rates were significantly lower for those receiving GCs than for those not receiving them. These findings were further supported by the observation that the retention rate of tocilizumab

TABLE 2 Logistic regression analysis for the possible association between baseline parameters and clinical, structural and functional remissions at 52 weeks by tocilizumab treatment

	Clinical remission		Structural remission		Functional remission	
Baseline clinical parameters	Chi-square	*P*-value	Chi-square	*P*-value	Chi-square	*P*-value
Age	13.39	0.0003	0.28	0.5966	24.89	<0.0001
Gender	2.81	0.0938	0.04	0.8507	0.17	0.6819
Disease duration	4.68	0.0305	0.63	0.4761	10.11	0.0015
DAS-28	15.74	<0.0001	1.86	0.1726	21.55	<0.0001
MMP-3	1.41	0.2354	1.59	0.2066	2.40	0.1211
Total vdH-Sharp score	0.73	0.3927	0.28	0.5966	4.75	0.0293*
Estimated yearly progression of total vdH-Sharp score	0.90	0.3416	13.18	0.0003	0.43	0.5131
HAQ-DI	24.52	<0.0001	4.21	0.0403	96.42	<0.0001
Comorbidity	0.06	0.8075	0.71	0.3987	0.79	0.3740
Dose of MTX	20.55	<0.0001	0.05	0.8187	6.92	0.0085
Dose of GCs	5.12	0.0237	5.75	0.0165	1.97	0.1609
Previous anti-TNFs	0.32	0.5736	0.44	0.5087	0.12	0.7279

TABLE 3 Multiple logistic regression models for the baseline parameters predictive of clinical, structural and functional remissions at 52 weeks of tocilizumab treatment

	Clinical remission		Structural remission		Functional remission	
Baseline clinical parameters	Adjusted odds ratio (95% confidence interval)	*P*-value	Adjusted odds ratio (95% confidence interval)	*P*-value	Adjusted odds ratio (95% confidence interval)	*P*-value
Duration, years	–	–	–	–	1.022 (0.987–1.061)	0.2295
DAS-28	0.673 (0.500–0.890)	0.0069	–	–	–	–
Estimated yearly progression of total vdH-Sharp score	–	–	0.967 (0.945–0.986)	0.0021	–	–
HAQ-DI	0.569 (0.359–0.886)	0.0141	0.624 (0.381–1.002)	0.0553	0.582 (0.360–0.919)	0.020
Dose of MTX, mg/week	1.134 (1.062–1.214)	0.0002	–	–	–	–
Dose of GCs, mg/day	0.898 (0.809–0.991)	0.0368	0.879 (0.786–0.978)	0.0202	–	–

treatment was higher for patients with MTX than for those without it, and lower for patients with GCs than for those without them. The question might be raised whether concomitant use of MTX and GCs is affected by a number of confounding factors. However, multivariate logistic regression analysis demonstrated that higher doses of MTX and lower doses of GCs, in addition to baseline DAS-28 and HAQ-DI, each independently contributed to achievement by tocilizumab of clinical remission at 52 weeks. The retention rates were not significantly different, and instead were consistent with our findings for DAS-28 and HAQ-DI at Week 52 in patients with and without these medications, suggesting that patients who do not achieve a satisfactory response or who have safety issues should discontinue tocilizumab.

The Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis, An IL-6 Inhibitor (SAMURAI) study demonstrated that, compared with DMARDs, tocilizumab monotherapy significantly inhibited progression of structural damage in Japanese RA patients [21]. In addition, preliminary results reported from the Tocilizumab Safety and the Prevention of Structural Joint Damage (LITHE) study showed that, compared with MTX alone, tocilizumab plus MTX treatment resulted in significantly less progression of joint destruction [22]. In the present study, X-ray images at baseline and at Week 52 of tocilizumab treatment were available for 149 of 232 patients, allowing us to evaluate the radiographic effect of tocilizumab. The radiographic data obtained in this study are consistent with the results of previous clinical trials, and the multivariate logistic regression analysis suggested the new hypothesis that concomitant GCs compromise the inhibition of structural progression by tocilizumab. As stated above, the duration of disease in patients enrolled in this study