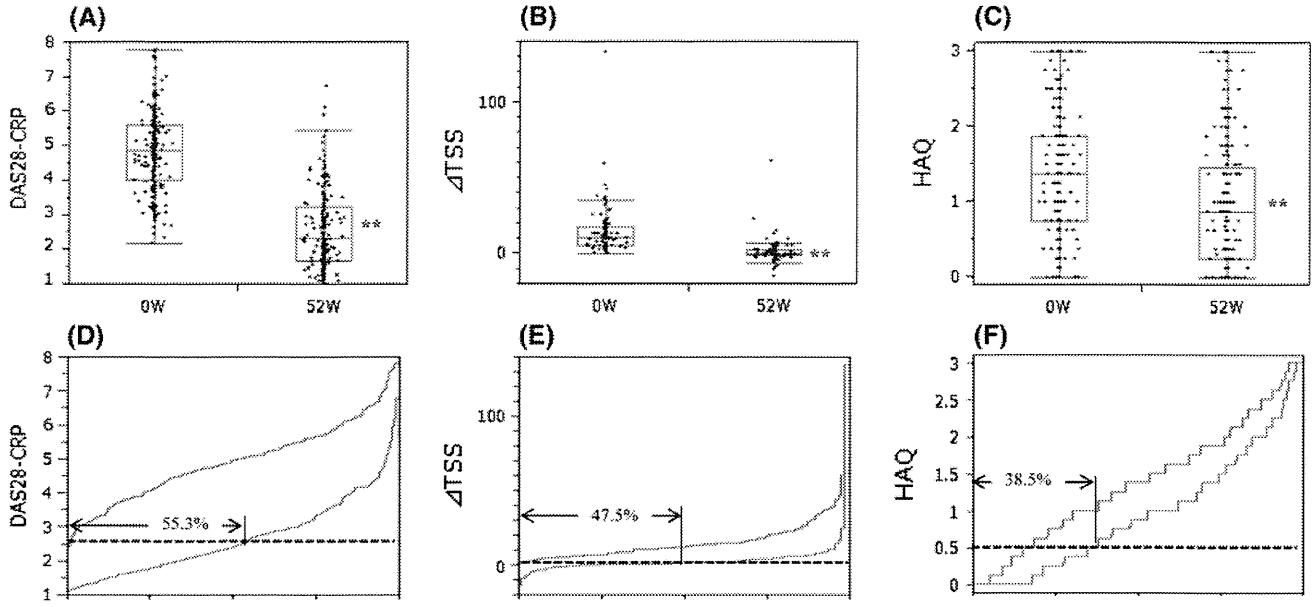

Fig. 1 Disease Activity Score for 28 joints (DAS28) values (**a**, **d**), yearly progression of modified total Sharp score (mTSS) (**b**, **e**), and Health Assessment Questionnaire Disability Index (HAQ-DI) values (**c**, **f**) in patients with rheumatoid arthritis (RA) at 0 and 54 weeks after the 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

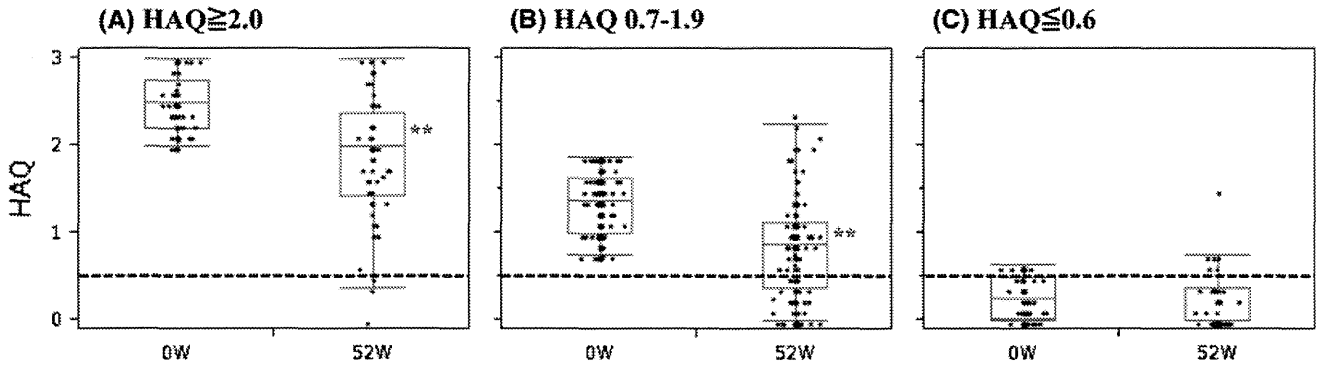

Fig. 2 Changes in Health Assessment Questionnaire (HAQ) values divided by baseline HAQ values before and after treatment with etanercept. One-way analysis of HAQ at 52 weeks after treatment by HAQ at 0 weeks, >2.0;upper 25th percentile of HAQ values (**a**); <0.6, lower 25th percentile (**c**); and between 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

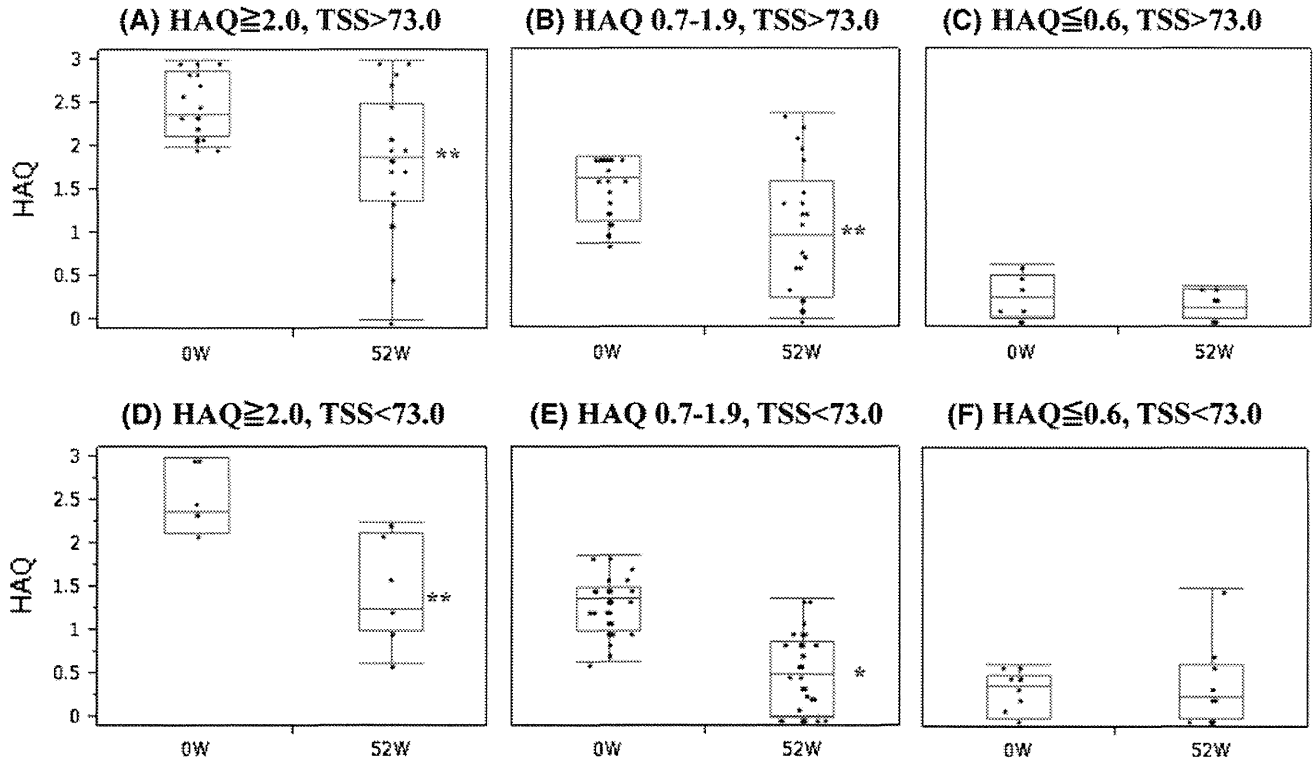

Fig. 3 Changes in Health Assessment Questionnaire (HAQ) values divided by baseline HAQ values and modified total Sharp score (mTSS) values before and after etanercept treatment; one-way analysis of HAQ at 52 weeks after treatment, at 0 weeks, >2.0; upper 25th percentile of HAQ values and >73.0; upper 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

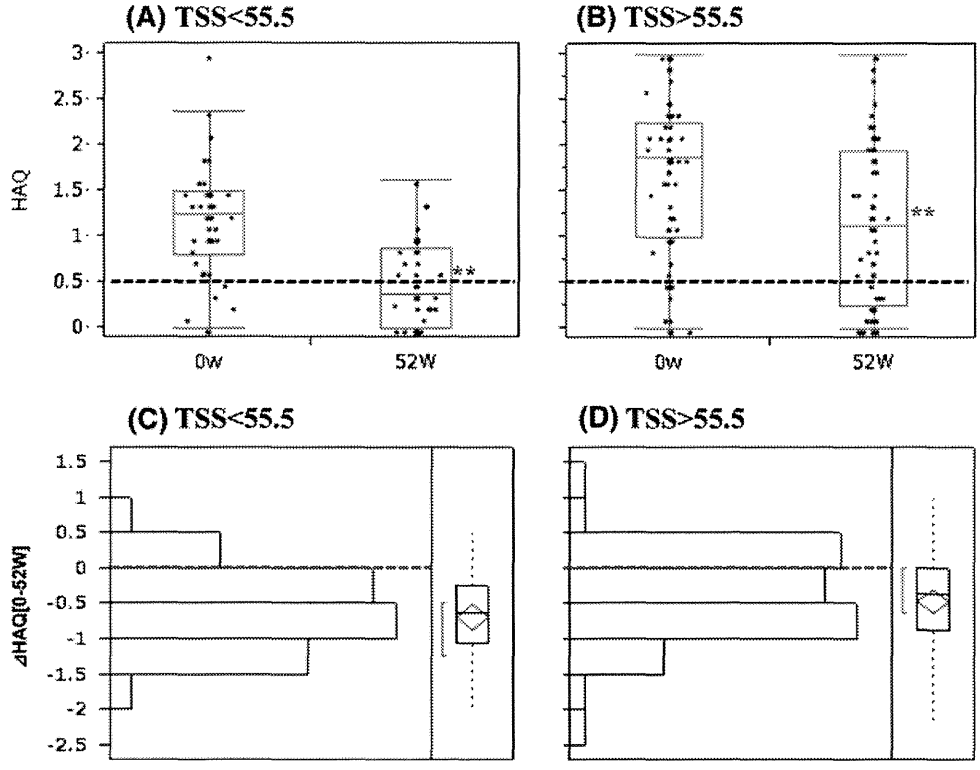

Fig. 4 Changes of Health Assessment Questionnaire (HAQ) values, divided by baseline modified total Sharp score (mTSS) values before and after initiation of etanercept treatment. From receiver operating characteristic (ROC) curve based on logistic regression analysis, the cutoff point of mTSS before treatment 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

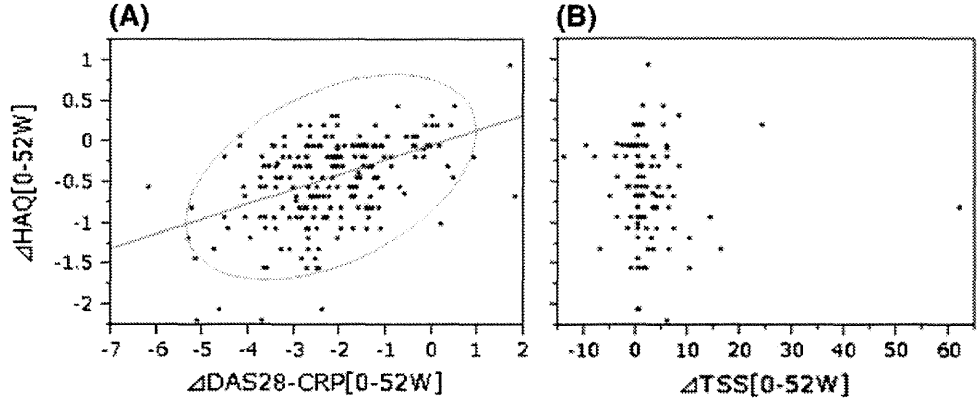

Fig. 5 Correlation between estimated yearly progression in Health Assessment Questionnaire Disease Index (ΔHAQ-DI) and Disease activity Score for 28 joints (ΔDAS28) (**a**) and between ΔHAQ-DI and modified total Sharp score (ΔmTSS) (**b**). *Dot plot* represents an individual value, and the *circle* 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

Incidence of serious respiratory infections in patients with rheumatoid arthritis treated with tocilizumab

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Abstract We aimed to demonstrate the incidence of serious respiratory infections in patients with rheumatoid arthritis (RA) treated with tocilizumab (TCZ) monotherapy. We analyzed the incidence of serious respiratory infections in 601 RA patients enrolled in TCZ clinical trials and their extension studies (TCZ cohort) and in 601 age- and sex-standardized RA patients treated in daily clinical practice at Tokyo Women's Medical University (IORRA subsample cohort). The rates of serious respiratory infections were 1.77 per 100 patient-years from 1999 to 2008 in the TCZ cohort and 0.53 per 100 patient-years from 2000 to 2009 in the IORRA subsample cohort. With the IORRA subsample cohort regarded as a standard population, the standardized incidence ratio (SIR) of serious respiratory infection in the TCZ cohort was 3.64 [95% confidence interval (CI) 2.56–5.01], standardized for age and sex; 2.35 (95% CI 1.66–3.24), standardized for age sex, and corticosteroid use; 1.85 (95% CI 1.30–2.55), standardized for age sex, and pre-existing pulmonary involvement; and 2.41 (95% CI 1.68–3.34) standardized for age sex, and disease activity. The risk of serious respiratory infection in the TCZ cohort was approximately double that in the IORRA subsample cohort after standardizing for corticosteroid use, pre-existing pulmonary involvement, or disease activity. This is comparable to the risk reported when tumor necrosis factor (TNF) inhibitors are used.

Keywords Rheumatoid arthritis · Tocilizumab · Pneumonia · Infection

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Introduction

Respiratory infection is a major complication that needs to be monitored in the treatment of rheumatoid arthritis (RA) in daily practice. Many epidemiological studies have shown patients with RA to have high morbidity and mortality from respiratory infection in relation to disease activity or corticosteroid use [1–5]. Recently, biologic agents such as anti-tumor necrosis factor (TNF) agents and other classes of agents have been introduced for the treatment of RA and patient outcome has been dramatically improved with them [6]. However, it is of serious concern whether these agents increase the risk of infection, especially respiratory infections [7–10]; most of the data in these studies were derived from anti-TNF agents. In Japan, postmarketing surveillance (PMS) studies have demonstrated the incidence and risk factors for respiratory infections in all patients treated with infliximab [11] and etanercept [12] registered in the all-case PMS registry, a unique registry conducted under the auspices of the Japan College of Rheumatology. However, because these studies included no control group, they were unable to demonstrate whether the incidence of respiratory infection was higher than that in RA patients treated without these biologics.

Tocilizumab (TCZ) is a humanized anti-interleukin (IL)-6 receptor (IL-6R) monoclonal antibody that effectively inhibits the activity of IL-6. TCZ has been approved in Japan for the treatment of RA since 2008. Randomized

controlled clinical trials have demonstrated that TCZ attenuates the signs and symptoms of RA [13–15] and prevents radiographic progression [16]. TCZ reduced RA disease activity even in patients who were refractory to disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX) [17], as well as in those who were refractory to anti-TNF agents [18]. Serious infectious events in patients treated with TCZ were infrequently detected, and, in short-term clinical trials, the rate of serious infections was reported to be a little bit higher than that in control patients [16, 17, 19]. However, the results of the safety profiles in clinical trials should be assessed carefully in the daily practice of rheumatology, because patients with relatively better condition may have been enrolled in these controlled trials and the length of the observational term may not have been sufficient to judge the safety.

Here, we report a long-term case–control study we conducted to investigate the risk of serious respiratory infections among 601 RA patients who were treated with TCZ in controlled studies and their extensions [20, 21] and 601 RA patients in daily clinical practice at Tokyo Women's Medical University. We investigated whether TCZ was associated with an increased risk of serious respiratory infections compared to RA patients in daily practice.

Patients and methods

This study was based on a comparison of two independent cohorts; one from TCZ controlled trials and their extensions, and the other, a subsample of a cohort of patients with RA treated at the Institute of Rheumatology, Tokyo Women's Medical University.

TCZ cohort

The TCZ cohort consisted of RA patients who participated in 6 clinical trials of TCZ and their extensions, including a phase I/II open-label dose-escalation study [13], a phase II multicenter double-blind dose-finding study [14], a phase III open-label randomized study (SAMURAI) [16], a phase III double-blind study (SATORI) [15], a drug–drug interaction study, and a renal failure study. The precise eligibility criteria for each study were described elsewhere [13–16, 20, 21]. Briefly, patients were ≥20 years old and fulfilled the 1987 American Rheumatism Association Criteria for RA [22] with a disease history of more than 6 months. All patients had failed to respond to previous treatments with at least one DMARD including MTX. At enrollment, the patients had active RA, as defined by the presence of six or more tender joints and swollen joints and an erythrocyte sedimentation rate (ESR) of ≥30 mm/h or C-reactive protein (CRP) level of ≥1.0 or 2.0 mg/dl according to the trial. Patients were allowed to take corticosteroids (≤10 mg/day as prednisolone). Among the 657 RA patients who were initially enrolled in the six clinical studies and/or their extension studies [20, 21], 601 patients received at least one dose of TCZ within the framework of these studies. TCZ was planned to be introduced as monotherapy in these studies. All the patients received either placebo or 2, 4, or 8 mg/kg body weight of TCZ in the initial study and 8 mg/kg body weight of TCZ in the extension study. Patients receiving a corticosteroid dose of ≤10 mg/day as prednisolone at entry to the initial study were permitted to continue corticosteroid treatment. Surgical treatment and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids was allowed, but concomitant use of DMARDs and immunosuppressive treatments was excluded. The period of observation was from August 1999 to August 2008.

The IORRA subsample cohort

The IORRA cohort is a large observational cohort of RA patients seen in daily practice at the Institute of Rheumatology, Tokyo Women's Medical University since October 2000. The characteristics of the IORRA cohort have been described elsewhere [5, 23–25]. Briefly, all patients diagnosed as having RA were registered in the IORRA cohort after informed consent was obtained, and they were asked to complete and submit a question sheet at the outpatients' clinic. They were asked to participate in the IORRA survey biannually (April and October) while they were being treated at our institute at these times. Parameters evaluated included patient assessment of pain and global evaluation by the visual analogue scale (VAS) and disability as measured by the Japanese Health Assessment Questionnaire (J-HAQ), which was validated in 2003 [26]; physician evaluation of disease activity (swollen joint count, tender joint count, and physician's assessment by VAS); and the following clinical parameters: ESR, CRP, and rheumatoid factor (RF). Patients also self-reported the use of drugs, such as corticosteroids (frequency and dose converted to prednisolone equivalent) and DMARDs including MTX and their doses. More than 5000 patients with RA were involved in each phase of the survey, and more than 98% of the patients submitted completed questionnaires by pre-paid mail.

As a control group for this long-term study, 601 RA patients matched by age and sex to the TCZ cohort, by a time-matching method, were selected from among the patients enrolled in the IORRA cohort. To attain 1:1 matching, one patient was selected from candidates using random numbers. Patients who had ever been treated with TCZ were excluded. The period of observation was from

October 2000 to April 2009. The baseline data of each patient in this subsample cohort were obtained at the first enrollment of the IORRA survey.

Determination of respiratory infection in this study

TCZ cohort

As indicated above, the TCZ cohort comprised patients who were enrolled in any of the six specified clinical trials and their extensions; therefore, any events occurring in these patients during the follow-up periods were picked up intensively all the way from the initiation of trial to the end of the observation period. "Serious" respiratory infections that occurred in the patients who took at least one dose of TCZ were defined according to the decisions of the affiliated doctors and were assessed based on the data of the clinical trials and extension studies from August 1999 to August 2008 [20].

IORRA subsample cohort

To detect respiratory events in the 601 patients of the IORRA subsample cohort from October 2000 to April 2009, the corresponding medical records of the 601 patients were abstracted and reviewed by trained rheumatologists for evidence of definite respiratory infections. A respiratory infection that required hospitalization was defined as a "serious" respiratory infection in the IORRA subsample cohort in this study.

Statistics

The number of serious respiratory infections per 100 person-years was calculated in each cohort. Taking the incidence of serious respiratory infections in the IORRA subsample cohort as basic data, the standardized incidence rate (SIR) and 95% confidence intervals (CIs) of serious respiratory infection in the TCZ cohort were analyzed. This analysis was performed again when standardized for treatment with corticosteroid at enrollment in the TCZ trials, or at first document of the IORRA survey, and first enrollment at for each patient standardized for the presence or absence of pre-existing pulmonary complications, including chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). The R version 2.10 software (Vienna, Austria) was used for the statistical calculations.

Results

The baseline characteristics of the RA patients in the TCZ cohort and in the IORRA subsample cohort are listed in Table 1. Patients in the TCZ cohort tended to have shorter disease duration but higher disease activity and greater physical dysfunction. Patients in the TCZ cohort had a high frequency of taking MTX and a high frequency and dose of corticosteroids at entry to the clinical trials. With respect to comorbidity, the coexistence of diabetes mellitus was more frequent in patients in the TCZ cohort, but the pre-existence of pulmonary disease was not different in the two cohorts.

Table 2 shows the incidence of serious respiratory infections in each cohort. Among the 601 patients in the TCZ cohort, 37 serious respiratory infections were identified in 2090.8 patient-years. Serious respiratory infections in the TCZ cohort included 28 cases (76%) of bacterial pneumonia, 2 cases of non-tuberculous mycobacterial infection, 2 cases of pulmonary fungal infection, 2 cases of tuberculosis, and 1 case of *Pneumocystis* pneumonia (PCP). On the other hand, 14 serious respiratory infections were identified among the 601 control patients in 2653.3 patient-years in the age- and sex-standardized IORRA subsample cohort; there were 10 cases (72%) of bacterial pneumonia, 2 cases of pulmonary fungal infection, and 1 case of PCP. The crude incidence rate of serious respiratory infections in the TCZ group was 1.77 per 100 patient-years, while that in control group was 0.53 per 100 patient-years

Table 1 Characteristics of the tocilizumab (TCZ)-treated cohort and the age- and sex-standardized IORRA subsample cohort

	TCZ n = 601	IORRA subsample n = 601
Age (years)	53.1 ± 11.4	53.4 ± 11.6
Women (%)	80.5	80.5
Duration (years)	6.5 ± 7.1	8.2 ± 7.6
ESR (mm/h)	63.0 ± 30.6	33.8 ± 23.9
CRP (mg/dl)	4.0 ± 3.0	1.3 ± 1.9
DAS28	6.3 ± 1.0	3.7 ± 1.3
mHAQ	0.88 ± 0.60	n.a.
J-HAQ	n.a.	0.72 ± 0.73
Diabetes mellitus (%)	10	4
Pulmonary disease (%)	5.7	5.2
Methotrexate (%)	91[a]	48
Methotrexate dose (mg/week)	n.a.	6.7 ± 2.9
Corticosteroids (%)	90.8	52.4
Prednisolone (mg/day)	6.7 ± 2.5	5.1 ± 3.0

Results are presented as means ± SD or percentages as appropriate

IORRA observational cohort of rheumatoid arthritis patients seen in daily practice at the Institute of Rheumatology, Tokyo Women's Medical University, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* disease activity score in 28 joints, *n.a.* not applicable, *mHAQ* modified Health Assessment Questionnaire, *J-HAQ* Japanese version of HAQ

[a] Methotrexate (MTX) use at entry to clinical trial

Table 2 Serious respiratory infections in the tocilizumab cohort and the IORRA subsample cohort

	TCZ 2090.8 person-years	IORRA subsample 2653.3 person-years
Serious respiratory infections	37	14
Bacterial pneumonia	28 (76%)	10 (72%)
Acute bronchitis	1 (3%)	0 (0%)
Acute exacerbation of chronic bronchitis	1 (3%)	0 (0%)
Chlamydial pneumonia	0 (0%)	1 (7%)
Pulmonary fungal infection	2 (5%)	2 (14%)
Pneumocystis pneumonia	1 (3%)	1 (7%)
Pulmonary tuberculosis[a]	2 (5%)	0 (0%)
Non-tuberculous mycobacterial infection	2 (5%)	0 (0%)

[a] Pulmonary tuberculosis including miliary tuberculosis

(Table 3). The age- and sex-standardized risk of serious respiratory infection in patients treated with TCZ was >3 times that in RA patients in daily practice receiving treatments other than TCZ (SIR 3.64, 95% CI 2.56–5.01). Taking the IORRA subsample cohort as basic data, the SIR of serious respiratory infection for patients treated with TCZ was recalculated after being standardized for potential confounders: SIR was 2.35 (95% CI 1.66–3.24) after being standardized for corticosteroid use, 1.85 (95% CI 1.30–2.55) after being standardized for pre-existing pulmonary involvement, and 2.41 (95% CI 1.68–3.34) after being standardized for disease activity evaluated by the disease activity score in 28 joints (DAS28).

Discussion

In this study, we have presented the first results concerning the incidence of serious respiratory infections in Japanese RA patients treated with TCZ and in patients treated in daily practice. The incidence of serious respiratory infections in Japanese RA patients in daily practice was 0.53 per 100 patient-years, whereas the incidence of serious respiratory infections in Japanese patients with RA treated with TCZ was 1.77 per 100 patient-years. We also found an approximately two-fold increase in the risk of incidence of serious respiratory infections in RA patients treated with TCZ compared to that of RA patients treated in daily practice after standardizing for pre-existing pulmonary involvement.

The risk of infection, especially pneumonia, has been reported to be higher in patients with RA than in the non-RA population. Doran et al. [1] followed a cohort of Minnesota residents comprising 609 RA patients and 609 non-RA study subjects for 12 years until 2000; they reported the incidence of pneumonia to be 4.02 per 100 patient-years in the RA patients and 2.39 per 100 patient-years in the non RA subjects. Smitten et al. [2] reported that the incidence of pneumonia requiring hospitalization was 0.84 per 100 patient-years in RA patients, but 0.36 per 100 patient-years in the control group; the data for their study was from the nationwide PharMetrics integrated claims database, which includes information (claim data) from fully adjudicated pharmacies, providers, and facilities for members enrolled in 61 health plans across the United States. Thus, the incidence rate of serious respiratory infections in Japanese RA patients that we report for the first time in this study is comparable to the rates previously reported.

In the present study, the SIR of serious respiratory infection obtained simply by age- and sex-standardized comparison was high (SIR 3.64), but after standardization for corticosteroid use or pre-existing pulmonary involvement, the SIR of serious respiratory infection dropped down to around 2 (1.85–2.35). We note that this study may have some biases and limitations. First, serious respiratory infection in the IORRA subsample cohort may have been underestimated compared to that in the TCZ cohort. Definite respiratory infections that required hospitalization were selected in the IORRA subsample cohort, whereas respiratory infections defined as "serious" by affiliated doctors were selected in the TCZ cohort irrespective of hospitalization. Second, the methods of reporting the incidence of respiratory infection were also somewhat different in the TCZ cohort and observational IORRA cohort; every single event that happened in the TCZ cohort was reported, whereas only events written in medical charts were reported in the IORRA subsample cohort. Third, we could not completely standardize for the patients' backgrounds in these two cohorts, especially with respect to disease activity and comorbidity. Therefore, it it is possible that the true SIR of serious respiratory infection in RA patients treated with TCZ may be somewhat lower than the results obtained in this study.

Because TCZ exerts its anti-rheumatic effect in patients who have failed to respond to anti-TNF agents [18], it is very interesting to investigate whether the effects on infection exerted by this anti-IL-6 agent differ from those shown by anti-TNF agents. Several investigators have reported that the use of anti-TNF agents increases the risk of infection, with the risk ranging from 1.2 to 5.6 [9, 10, 27–31]. Results from randomized controlled trials are useful in eliminating some of the biases inherent in registries; however, the careful subject selection and screening in randomized trials may lead to inaccurate estimations of results in the real world. Considering these points of view, the risk of serious respiratory infection in patients treated

Table 3 Standardized incidence ratio (SIR) of serious respiratory infection in patients treated with tocilizumab in clinical trials and their extension studies in comparison with patients treated in daily clinical practice

	Standardization	Events (*n*)	Person-years	Crude incidence rate (/100 person-years)	SIR
TCZ	Age × sex	37	2090.8	1.77	3.64[a] (2.56–5.01)
IORRA subsample		14	2653.3	0.53	
TCZ	Age × sex + steroid	37	2090.8	1.77	2.35[b] (1.66–3.24)
IORRA subsample		14	2653.3	0.53	
TCZ IORRA subsample	Age × sex + pulm involv	37	2090.8	1.77	1.85[c] (1.30–2.55)
		13	2596.5	0.50	
TCZ	Age × sex + disease activity	35	2008.1	1.74	2.41[d] (1.68–3.34)
IORRA subsample		13	2505.9	0.52	

[a] Standardized incidence ratio (SIR) compared with patients in the IORRA subsample cohort standardized for age and sex

[b] SIR compared with patients in the IORRA subsample cohort standardized for age, sex, and corticosteroid use

[c] SIR compared with patients in the IORRA subsample cohort standardized for age, sex, and pre-existing pulmonary involvement (*pulm involve*) including chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD)

[d] SIR compared with patients in the IORRA subsample cohort standardized for age, sex, and disease activity (DAS28)

with TCZ may have the same burden as that in patients treated with anti-TNF agents.

In conclusion, the present study showed that, compared to RA patients treated in daily practice, there was an approximately two-fold increase in the risk of serious respiratory infection in RA patients treated with TCZ after standardization for the use of corticosteroids or for pre-existing pulmonary involvement. This is comparable to the risk reported for TNF inhibitors, so signs of infection should be carefully monitored during therapy with biologics.

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Conflict of interest NN has served as a medical adviser to and received a consulting fee from Chugai Pharmaceutical Co. Ltd., the manufacturer of TCZ. He also received a royalty for the patent of TCZ used for systemic juvenile idiopathic arthritis. NN also works as a scientific adviser to F. Hoffmann-La Roche, which is developing TCZ in collaboration with Chugai Pharmaceutical Co., Ltd. H. Yamanaka received Research support from: Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Wyeth K. K., Daiichi Sankyo Co., Ltd., Banyu Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Abbott Japan Co., Ltd., Eisai Co., Ltd., Santen Pharmaceutical Co.,Ltd., Taishotoyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited, Kissei Pharmaceutical Co., Ltd and Janssen Pharmaceutical K. K. H. Yamanaka is also a paid instructor for: Abbott, Eisai Co., Ltd., Takeda Pharmaceutical Company Limited, Mitsubishi Tanabe Pharma Corporation, Janssen Pharmaceutical K. K., Hoffmann-La Roche, Chugai Pharmaceutical Co., Ltd, and Pfizer Inc.

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ORIGINAL ARTICLE

Improvement of health status evaluated by Arthritis Impact Measurement Scale 2 (AIMS-2) and Short Form-36 (SF-36) in patients with rheumatoid arthritis treated with tocilizumab

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Abstract
Objective To evaluate the improvement of health status in patients with rheumatoid arthritis (RA) treated with tocilizumab.
Methods Thirty-nine patients were treated with 8 mg/kg tocilizumab every 4 weeks for 24 weeks. Disease activity was assessed by Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI). Improvement of health status was assessed by Arthritis Impact Measurement Scale 2 (AIMS-2) and Short Form-36 (SF-36).
Results Tocilizumab improved CDAI and SDAI significantly at week 4 compared with at baseline. In the components of AIMS-2, "physical score", "symptom" and "affect" improved significantly at week 4 compared with at baseline, while "social interaction" did not improve significantly during 24 weeks of tocilizumab therapy. Similarly in SF-36, "bodily pain", "general health", "vitality" and "mental health" improved significantly at week 4. The most correlative component of AIMS-2 with CDAI was "symptom", while "social interaction" did not correlate with CDAI during tocilizumab treatment.
Conclusion The time-course diversity in improvement of health status should be considered to provide proper healthcare when treated with tocilizumab.

Keywords Anti-IL-6 receptor antibody · Health status · IL-6 · QOL · RA

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent synovitis, resulting in destruction of cartilage and bone [1]. Persistent inflammation and bone destruction of multiple joints lead to impairment of physical, psychological and social condition [2]. Therefore, tight control with regular follow-up is recommended to prevent joint destruction and physical disability [3], and proper evaluation of health status of patients with RA is important.

Interleukin-6 (IL-6), a pleiotropic cytokine with a wide range of biological activities such as inflammation, immunological reactions and haematopoiesis, is involved in the pathogenesis of RA [4, 5]. Tocilizumab, an anti-IL-6 receptor monoclonal antibody, has been demonstrated to be

effective for improvement of disease activity and inhibition of progression in structural joint damage in patients with RA [6, 7]. As regards functional improvement, tocilizumab is reported to improve quality of life (QOL) of patients with RA in clinical trial [8]. However, there is no report investigating in detail how tocilizumab therapy improves health status of patients with RA in the daily clinical setting.

Arthritis Impact Measurement Scale 2 (AIMS-2) is designed to measure various components of health status in patients with arthritis, and Short Form-36 (SF-36) is selected to measure generic health status. Both of these scales contain assessment of various phases of QOL such as symptom, physiological phase, physical phase and social phase. In this report, we assess the time course of improvement in health status of patients with RA treated with tocilizumab utilizing AIMS-2 and SF-36 in order to provide proper healthcare to patients treated with tocilizumab.

Table 1 Baseline characteristics of patients with rheumatoid arthritis treated with tocilizumab

Clinical variable	RA patients
Number of subjects	39
Age (years)	52.8 ± 12.8
Sex (female/male)	35/4
RA duration (years)	7.4 ± 8.1
Stage (I/II/III/IV)	4/19/11/5
Class (I/II/III/IV)	0/32/6/1
Tender joint count (28)	12.8 ± 7.2
Swollen joint count (28)	14.3 ± 9.8
CRP (mg/dl)	2.7 ± 2.8
DAS28-CRP	5.32 ± 1.17
CDAI	32.7 ± 13.3
SDAI	35.4 ± 14.3
MMP-3 (ng/ml)	285.5 ± 232.6
PSL (mg/day)	4.4 ± 3.8
MTX (mg/week)	5.6 ± 3.2
Previous anti-TNF treatment	22 (56.4 %)

PSL prednisolone, *MMP* matrix metalloproteinase

Patients and methods

Patients with active RA who were refractory to synthetic and/or biologic disease-modifying antirheumatic drugs (DMARDs) were enrolled in this study between April 2008 and October 2010. All patients fulfilled the 1987 revised criteria of the American College of Rheumatology for RA [9]. Patients in the NTT West Osaka Hospital and Yukioka Hospital were selected for enrolment with approval of the ethics committee of the hospitals, and informed consent was obtained from all patients. Increased dosage of oral glucocorticoid and methotrexate (MTX) was not allowed, nor the introduction of DMARDs throughout the study. Exclusion criteria included tuberculosis and hepatitis B virus infection.

The patients were treated with 8 mg/kg tocilizumab intravenously every 4 weeks until week 24. Disease activity of RA before tocilizumab therapy was evaluated by calculating Disease Activity Score 28 (DAS28)-C-reactive protein (CRP) [10], Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) [11]. Clinical response to the therapy was assessed by CDAI and SDAI every 4 weeks simultaneously as markers of disease activity of RA.

AIMS-2 is a questionnaire designed to measure various components of health status in patients with arthritis [12]. The core part of the questionnaire contains 57 items that are categorized in 12 scales, and these scales are summarized as five component scores: physical (mobility level, walking and bending, hand and finger function, arm function, self-care, household tasks), symptom (arthritis pain), role (work), social interaction (social activity, support from family and friends) and affect (level of tension, mood).

SF-36 is selected to measure generic health status [13] because of its reliability and validity among both disease

Table 2 Change of disease activity in patients with rheumatoid arthritis (RA) during 24 weeks of tocilizumab therapy

	Baseline	4 weeks	12 weeks	24 weeks
CDAI	32.7 ± 13.3	20.5 ± 11.2*	11.1 ± 8.5*	6.7 ± 5.9*
SDAI	35.4 ± 14.3	21.0 ± 11.3*	11.3 ± 8.6*	6.8 ± 5.9*
Tender joint count	10.9 ± 6.7	6.3 ± 5.0*	3.7 ± 3.6*	2.2 ± 3.0*
Swollen joint count	11.1 ± 6,1	6.8 ± 5.5*	3.1 ± 3.5*	1.5 ± 1.9*
Patient global assessment (cm)	5.2 ± 2.3	4.1 ± 2.3*	2.7 ± 1.9*	1.9 ± 1.6*
Evaluator global assessment (cm)	5.5 ± 1.9	3.3 ± 1.8*	1.5 ± 0.9*	1.1 ± 0.9*
CRP (mg/dl)	2.7 ± 2.8	0.5 ± 1.8*	0.2 ± 0.5*	0.1 ± 0.1*

Tocilizumab improved CDAI and SDAI significantly at week 4 compared with at baseline. Swollen joint counts, tender joint counts, patient global assessments, evaluator global assessment and CRP improved significantly at week 4 compared with at baseline

* $p < 0.05$ versus at baseline by Wilcoxon signed-rank test

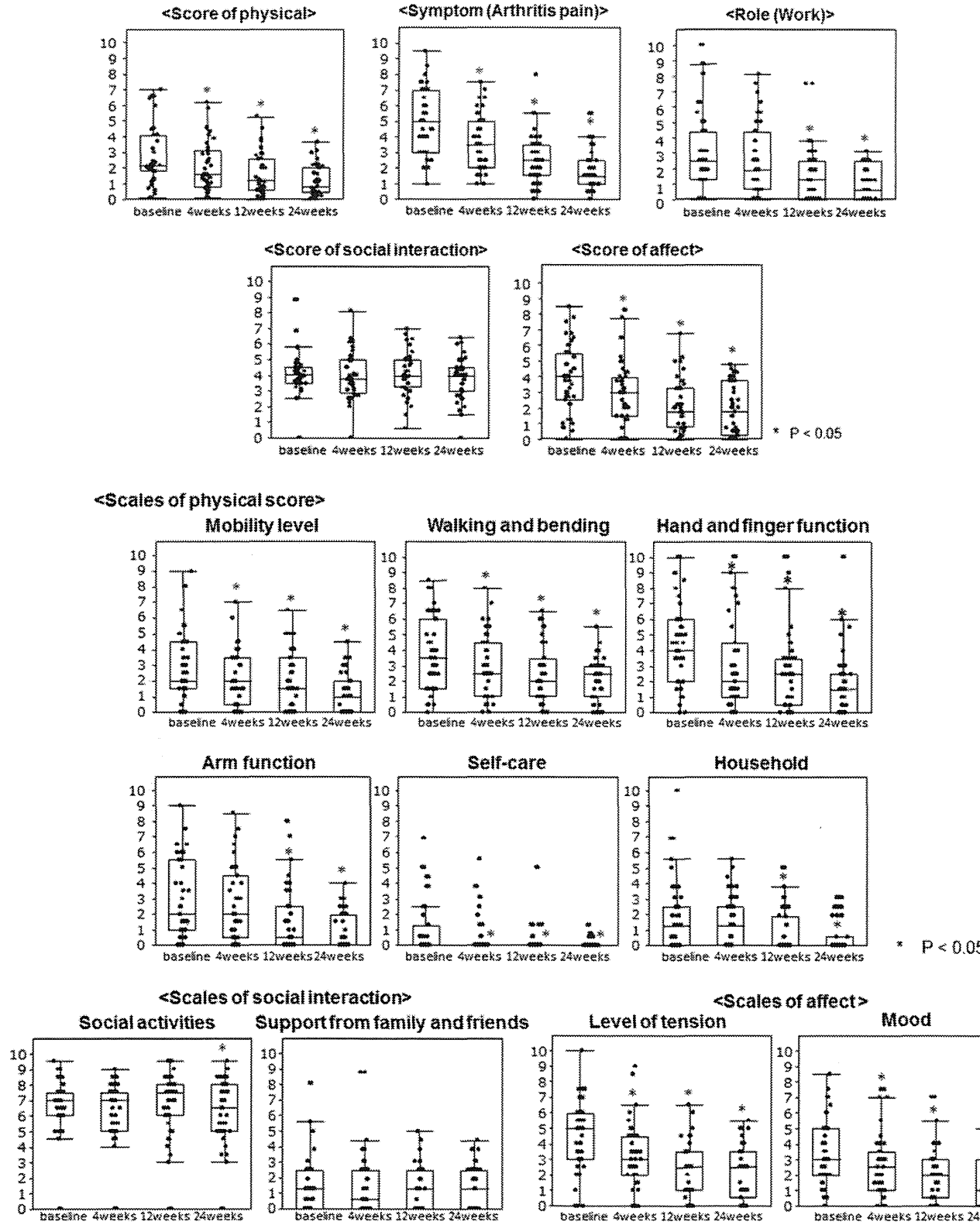


Fig. 1 Changes of health status by Arthritis Impact Measurement Scale 2 (AIMS-2) in patients with rheumatoid arthritis (RA) treated with tocilizumab. Tocilizumab improved the components and scales of AIMS-2 except "social interaction" and "support from family" significantly during 24 weeks of tocilizumab therapy compared with at baseline. *$p < 0.05$ versus at baseline by Wilcoxon signed-rank test

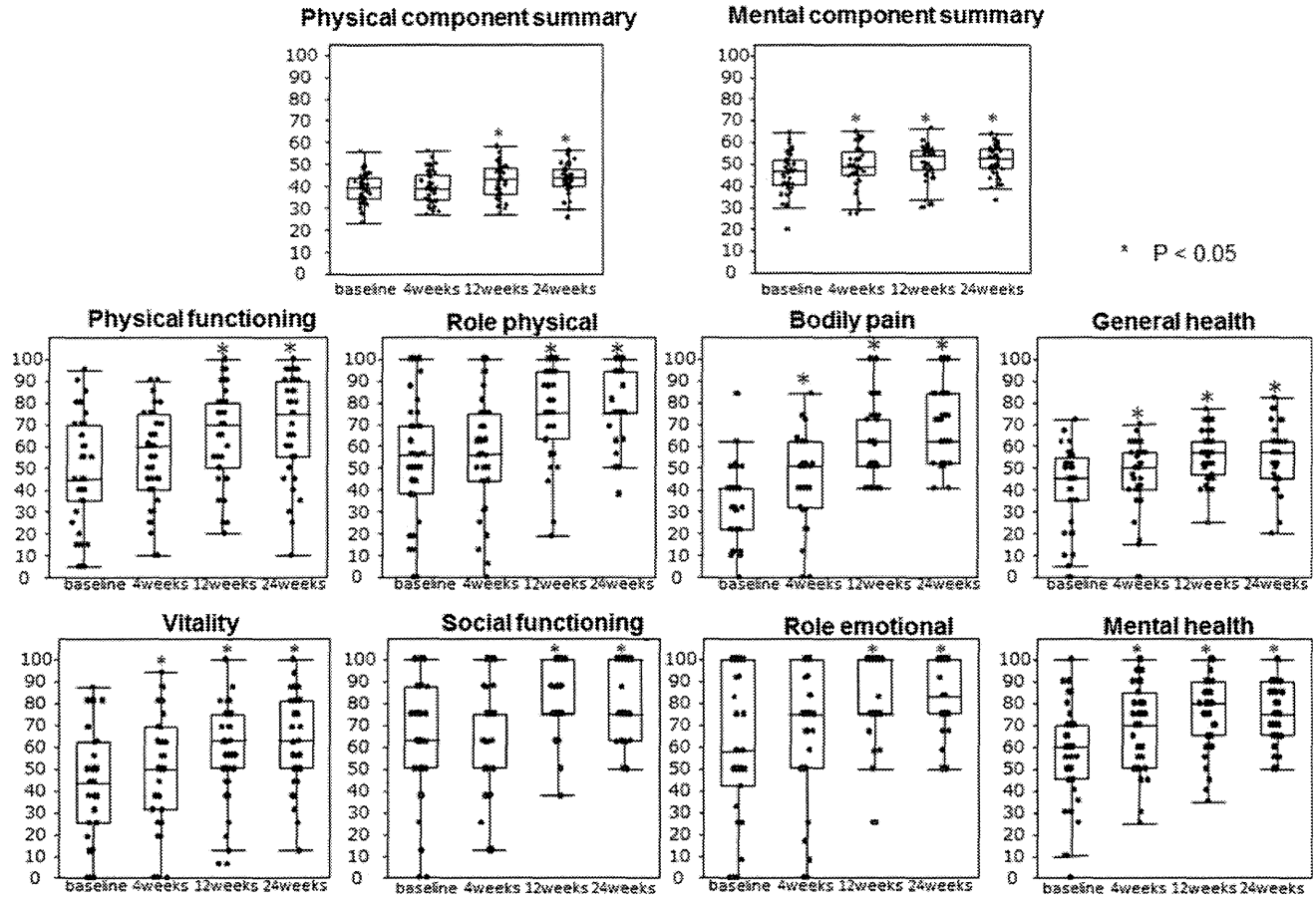


Fig. 2 Changes of health status by Short Form-36 (SF-36) in patients with rheumatoid arthritis (RA) treated with tocilizumab. Tocilizumab improved all scales of SF-36 significantly within 24 weeks of tocilizumab therapy compared with at baseline. *$p < 0.05$ versus at baseline by Wilcoxon signed-rank test

and general populations and its usefulness in comparing the health burden of different conditions and the benefits of treatment [14]. The SF-36 consists of 36 items, 35 of which are aggregated to score 8 dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Each SF-36 scale is scored using norm-based methods that standardize the scores to a mean of 50. Scores on the 8 SF-36 scales were further aggregated to produce physical component score (PCS) and mental component summary (MCS) measures of health status.

We measured AIMS-2 and SF-36 at week 0 as baseline and at week 4, 12 and 24 and, moreover, examined the correlation between the components and scales of AIMS-2 and CDAI in patients with RA at week 4, 12 and 24 during tocilizumab therapy.

Statistical analysis

Data analysis was performed utilizing non-parametric Wilcoxon signed-rank test. Pearson correlation analysis was used to calculate the correlation coefficient. Probability value of less than 0.05 was considered significant.

Results

Patient characteristics

Thirty-nine patients with RA (4 male and 35 female) were enrolled in this study. The characteristics of the patients are presented in Table 1. The mean ± standard deviation (SD) of age was 52.8 ± 12.8 years and that of disease duration was 7.4 ± 8.1 years. According to the Steinbrocker functional classification, 82 % of the patients were classified as class II, 15 % as class III and 3 % as class IV, while 10.3 % of the patients were classified as stage I, 48.7 % as stage II, 28.2 % as stage III and 12.8 % as stage IV. The mean ± SD of DAS28-CRP and those of CDAI and SDAI were 5.32 ± 1.17, 32.7 ± 13.3 and 35.4 ± 14.3, respectively. All enrolled patients had high or moderate disease activity at entry on DAS28-CRP,

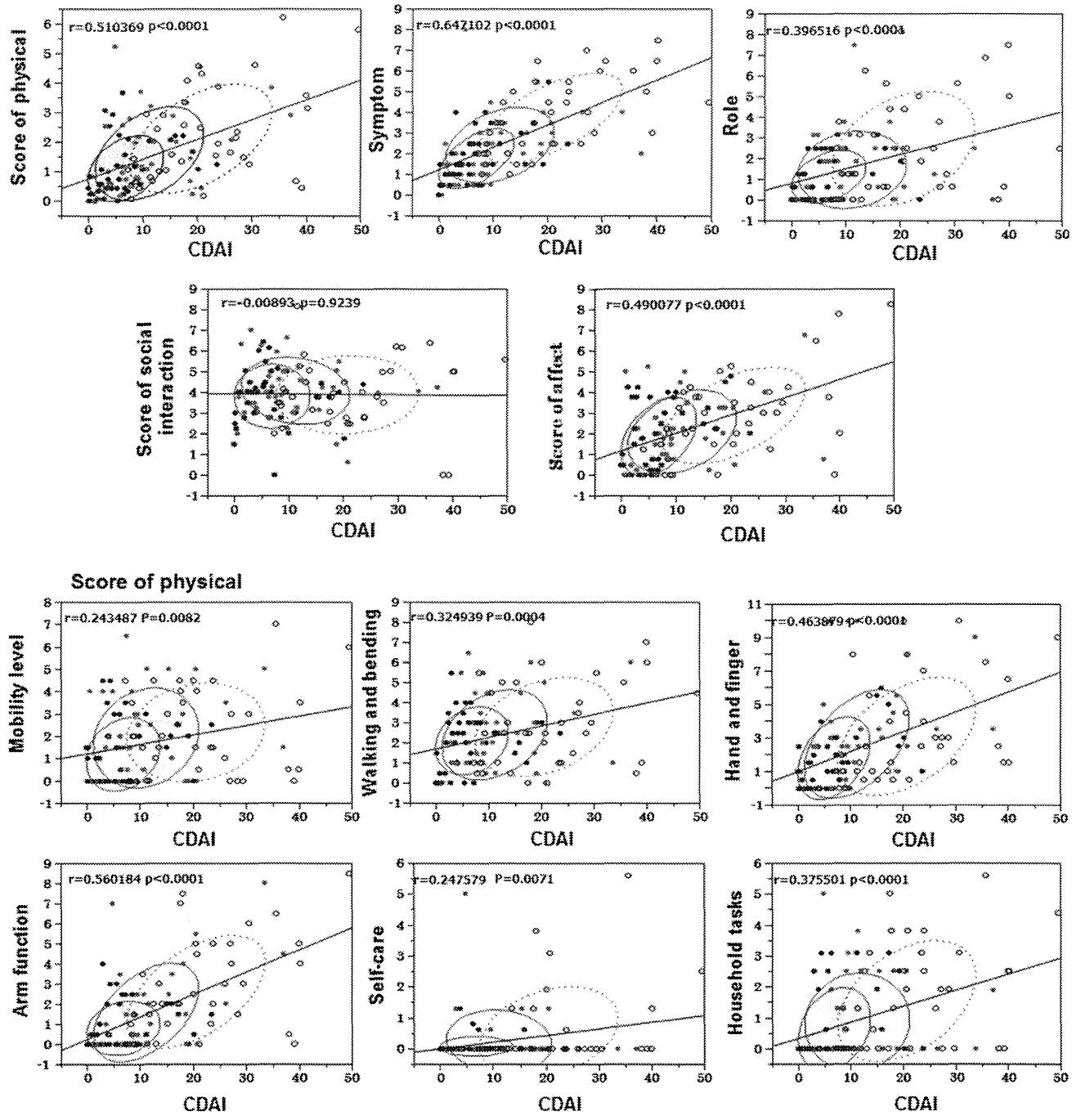


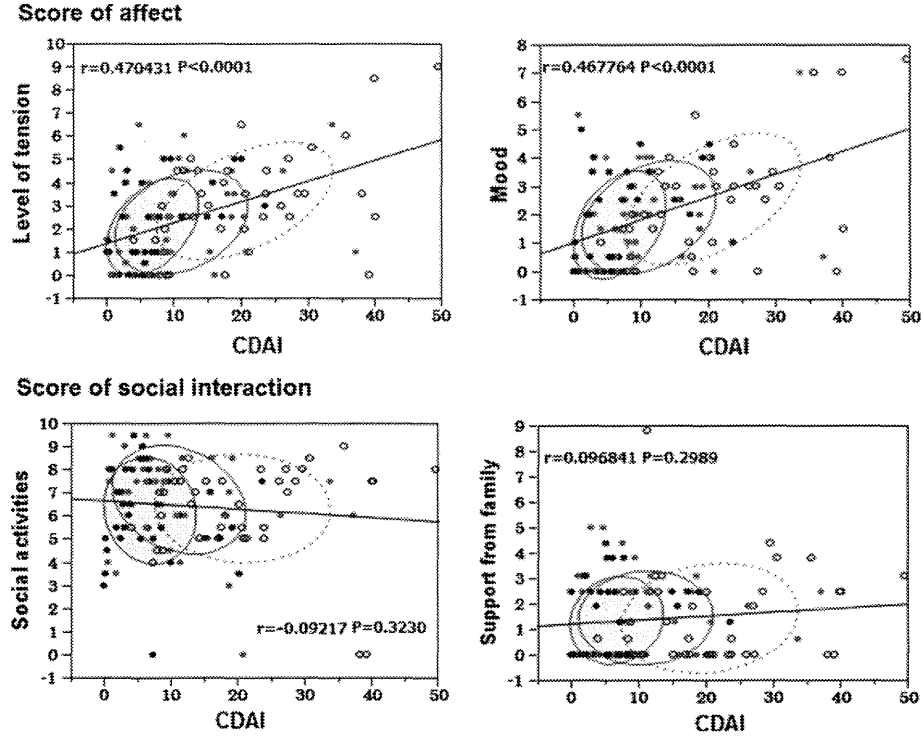
Fig. 3 Scatter plots of each item of AIMS-2 versus CDAI in patients with rheumatoid arthritis at week 4 (*open circles*), week 12 (*gray circles*) and week 24 (*closed circles*) after tocilizumab therapy. The Pearson coefficient of correlation between each item of AIMS-2 and CDAI is shown. "Symptom (pain)" has the strongest correlation among the items of AIMS-2 with CDAI ($r = 0.6471$, $p < 0.0001$). "Social interaction" and its two scales (social activity, support from family and friends) did not have any correlation with CDAI during tocilizumab therapy. The probability ellipsoids at week 4, 12 and 24 are shown in each circle

CDAI and SDAI. Twenty-seven (69.2 %) and 31 (79.5 %) patients were administrated prednisolone and MTX, respectively. Twenty-two (56.4 %) patients were previously treated with tumour necrosis factor (TNF) antagonists.

Improvement of disease activity during tocilizumab treatment

The improvement of swollen joint counts, tender joint counts, patient global assessment and evaluator global

Fig. 3 continued



assessment and CRP is shown in Table 2. Each score improved significantly at week 4 compared with at baseline. In 27 of 39 patients (69.2 %), CRP normalized at week 4.

CDAI and SDAI also improved significantly at week 4 compared with at baseline by tocilizumab therapy (Table 2). All of these scores continued to decrease during tocilizumab therapy, with mean CDAI and SDAI improving from 32.7 and 35.4 at baseline to 6.7 and 6.8 at week 24, respectively. At week 24, the remission rates of CDAI and SDAI were 28.2 and 33.3 %, respectively.

Improvement of health status evaluated by AIMS-2 during tocilizumab treatment

Change of health status in patients with RA was monitored utilizing AIMS-2 during tocilizumab therapy (Fig. 1). Among the five summary components, "physical", "symptom" and "affect" improved significantly at week 4 (median [range]; 2.17 [0.08–7], 5 [1–9.5], 4 [0–8.5] at baseline; 1.58 [0.08–6.21], 3.5 [1–7.5], 3 [0–8.25] at week 4, respectively). "Role" improved significantly at week 12 (median [range]; 2.5 [0–10] at baseline; 1.25 [0–7.5] at week 12). However, "social interaction" did not improve significantly within 24 weeks during tocilizumab treatment (median [range]; 4.06 [0–8.81] at baseline; 4 [0–6.44] at week 24). Most of the scales of AIMS-2 improved significantly, while the scale of "support from family and friends" did not improve during 24 weeks of tocilizumab treatment (median [range]; 1.3 [0–8.1] at baseline; 1.3 [0–4.4] at week 24).

Improvement of health status evaluated by SF-36 during tocilizumab treatment

Change of health status in patients with RA utilizing SF-36 during tocilizumab treatment is shown in Fig. 2. Among the eight scales, "bodily pain", "general health", "vitality" and "mental health" improved significantly at week 4 (median [range]; 41 [0–84], 45 [0–72], 43.8 [0–87.5], 60 [0–100] at baseline; 51 [0–84], 50 [0–70], 50 [0–94], 70 [25–100] at week 4, respectively). "Physical functioning", "role physical", "social functioning" and "role emotional" improved significantly at week 12 (median [range]; 45 [5–95], 56 [0–100], 62.5 [0–100] and 58.3 [0–100] at baseline; 70 [20–100], 75 [18.8–100], 75 [37.5–100] and 75 [25–100] at week 12).

Correlation between health status and disease activity during tocilizumab treatment

The correlation between each component and scale of AIMS-2 and CDAI in patients with RA was assessed at week 4, 12 and 24 after tocilizumab therapy started. The scatter plot of the results for each patient at week 4, 12 and 24 shows the correlations between each item of AIMS-2 and CDAI (Fig. 3). The Pearson coefficient of correlation between "symptom" and CDAI was the strongest among

the items of AIMS-2 ($r = 0.6471$, $p < 0.0001$). Most of the other subscales showed moderate correlation with CDAI. On the contrary, correlations between "social interaction" or its scales (social activity, support from family and friends) and CDAI were not observed during tocilizumab therapy ($r = -0.0089$, $r = 0.0921$ and $r = 0.0968$; $p = 0.9239$, $p = 0.3230$ and $p = 0.2989$, respectively). The probability ellipsoids at week 4, 12 and 24 suggest that "social interaction" and its scales (social activity, support from family and friends) were not improved despite the improvement of CDAI by tocilizumab treatment.

Discussion

The AIMS-2 subscales are responsive to change in health status, especially in the physical and pain dimensions, and are thought to be suitable for assessing change of health status in patients with RA when clinically treated [15]. In our study, among the five summary components of AIMS-2, "physical", "symptom" and "affect" improved significantly immediately after tocilizumab therapy, while "role" improved belatedly. Rapid improvement of "physical", "symptom" and "affect" was also reported when patients with RA were treated with infliximab [16]. All scales of the physical component improved significantly within 24 weeks of tocilizumab therapy, similarly to infliximab [17]. Meanwhile, "social interaction" did not improve significantly within 24 weeks during tocilizumab therapy, which was also comparable to previous study of infliximab treatment [17].

Meanwhile, when the health status in the same patients was assessed utilizing SF-36, "bodily pain", "general health", "vitality" and "mental health" improved significantly at week 4 and "physical functioning", "role physical", "social functioning" and "role emotional" improved significantly at week 12. In both assessments, "symptom (bodily pain)", "mental health" and "vitality" were proved to improve rapidly at week 4 with tocilizumab therapy, and "role" to improve belatedly. "Social functioning" also improved at week 12 in SF-36, while "social interaction" in AIMS-2 did not improve within 24 weeks of tocilizumab therapy. AIMS-2 is reported to be less responsive than SF-36 in the social function domain [18], and especially "social support" is reported not to improve significantly despite improvement of disease activity by treatment [19]. Therefore, the difference of improvement in social score between SF-36 and AIMS-2 depends on the different sensitivities of the measures.

Pain is the area of health in which almost 70 % of the patients would like to see improvement [20] and may still have sufficient impact on QOL to remain the top priority for improvement despite an improved level of pain [18]. In this study, tocilizumab improved "symptom" immediately at 4 weeks.

Moreover, we examined the correlation between health status and disease activity in patients with RA during tocilizumab therapy. The most correlative component of AIMS-2 with CDAI was "symptom". "Physical" and "affect" were moderately correlated and "social interaction" was not correlated with CDAI during tocilizumab therapy. These data suggest that tocilizumab improves disease activity of RA accompanied by improvement of "symptom" most correlatively, while "social interaction" does not always improve even if disease activity improves. The reason why symptom (pain) mostly correlated with disease activity is thought to be that all the components of CDAI except swollen joint counts are affected by pain of patients to varying degrees. Therefore, relieving pain is important for good QOL of patients with RA.

In conclusion, this is the first report in which improvement in health states of RA patients was evaluated utilizing two measures, AIMS-2 and SF-36, during tocilizumab therapy. Both measures indicate that "pain", "mental health" and "vitality" improved rapidly with tocilizumab therapy. As regards the correlation between health status and disease activity, "pain" is the most correlative component with disease activity. The limitation of this study is that it is a trial with a single arm and limited numbers in the daily clinical setting. Therefore, a controlled trial enrolling many subjects is desirable to confirm the result. We should consider the time-course diversity in the improvement of health status evaluated by AIMS-2 and SF-36 when newly treated with tocilizumab to understand the demands of patients with RA and provide proper healthcare while treating with biologics.

Conflict of interest None.

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