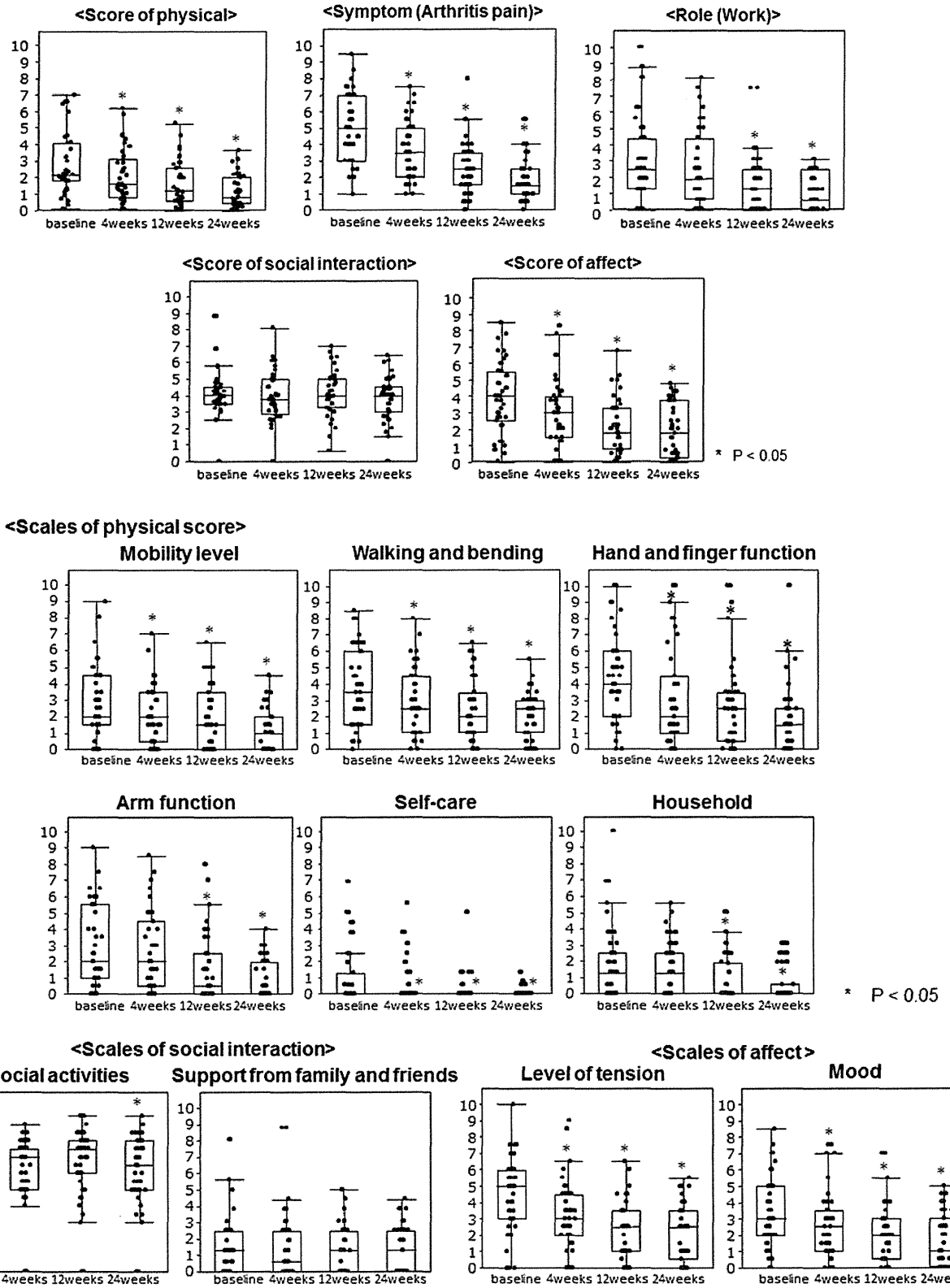


Fig. 1 Changes of health status by Arthritis Impact Measurement Scale 2 (AIMS-2) in patients with rheumatoid arthritis (RA) treated with tocilizumab. Tocilizumab improved the components and scales of AIMS-2 except "social interaction" and "support from family" significantly during 24 weeks of tocilizumab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

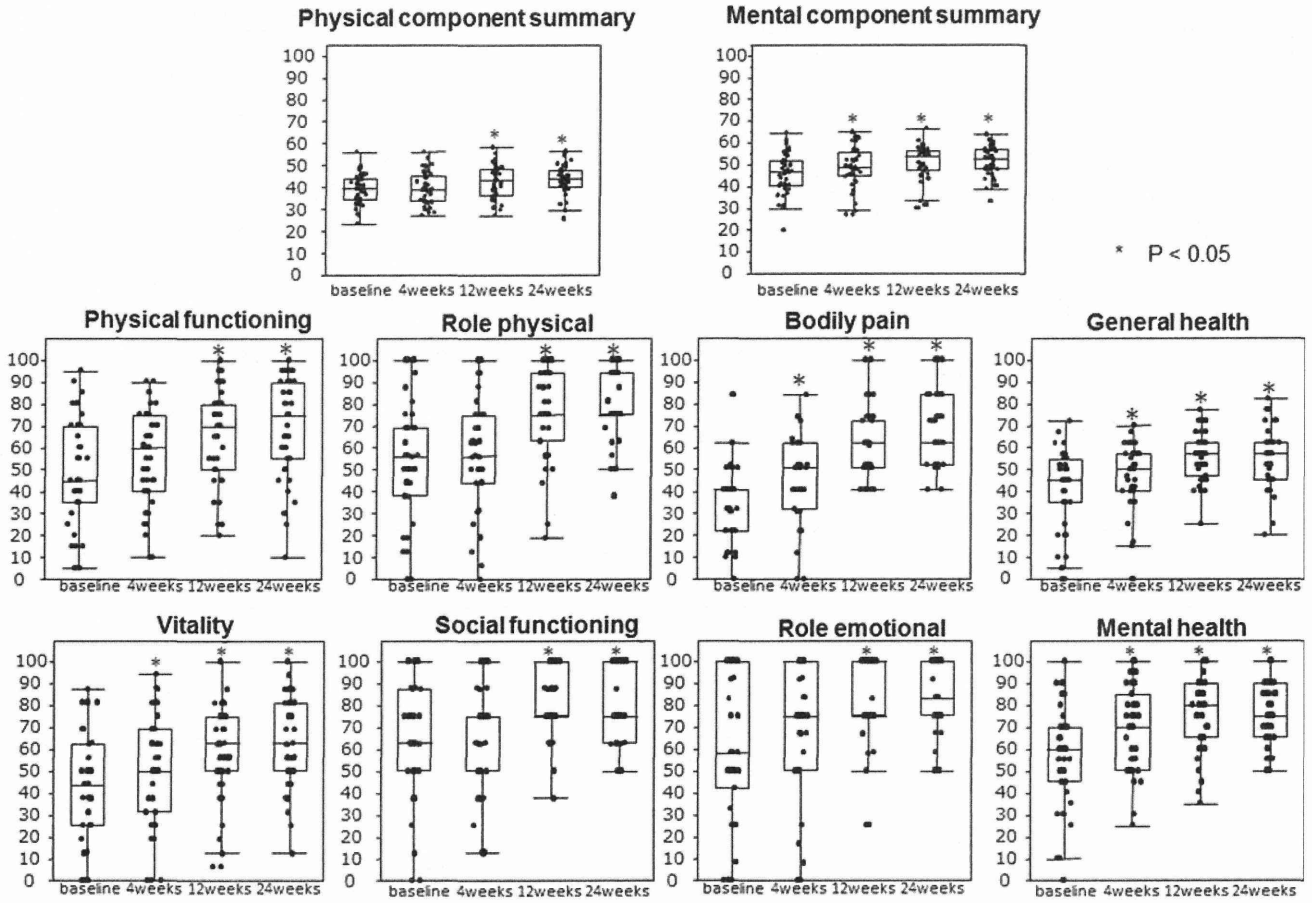


Fig. 2 Changes of health status by Short Form-36 (SF-36) in patients with rheumatoid arthritis (RA) treated with tocilizumab. Tocilizumab improved all scales of SF-36 significantly within 24 weeks of tocilizumab therapy compared with at baseline. *$p < 0.05$ versus at baseline by Wilcoxon signed-rank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

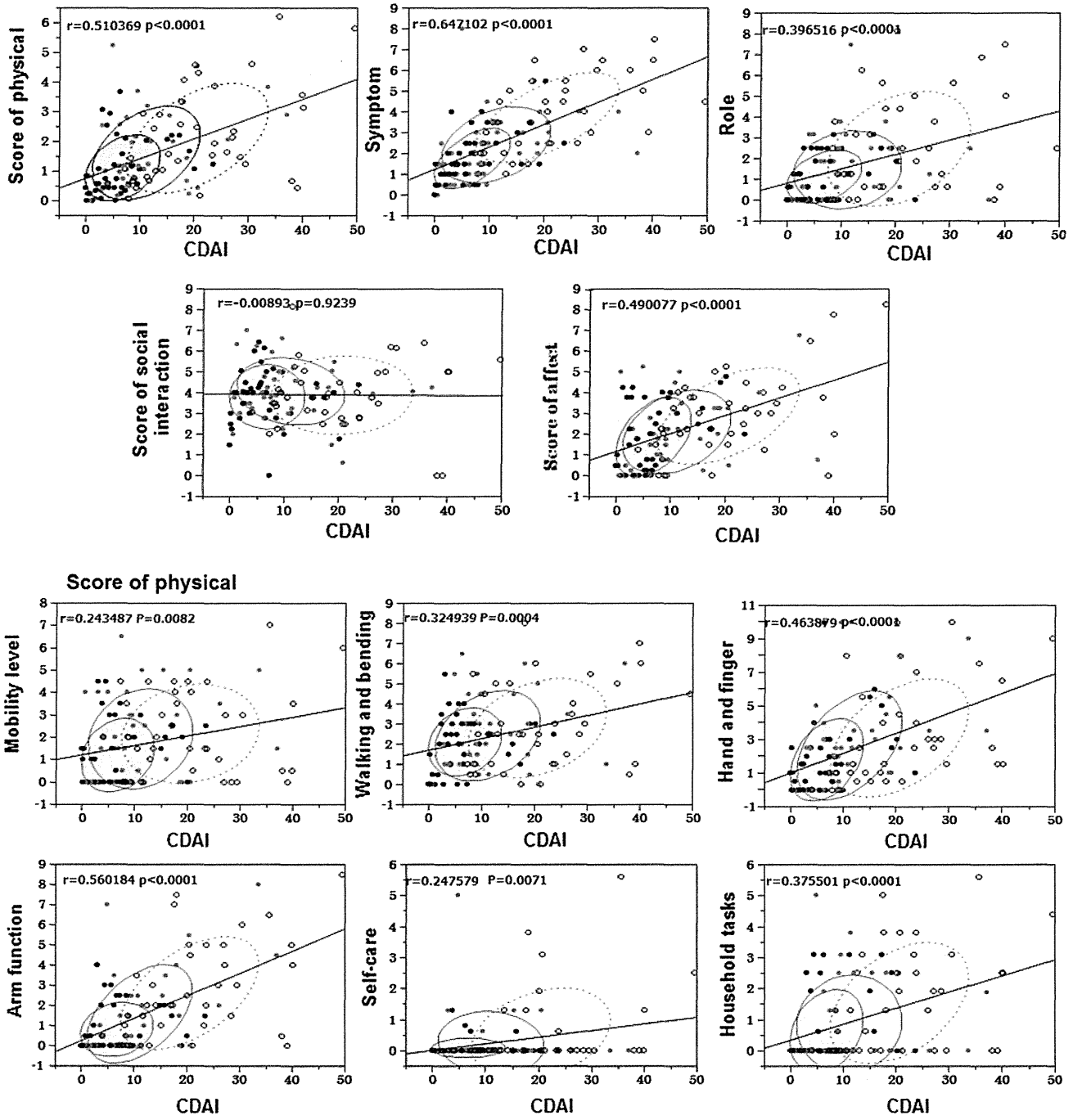


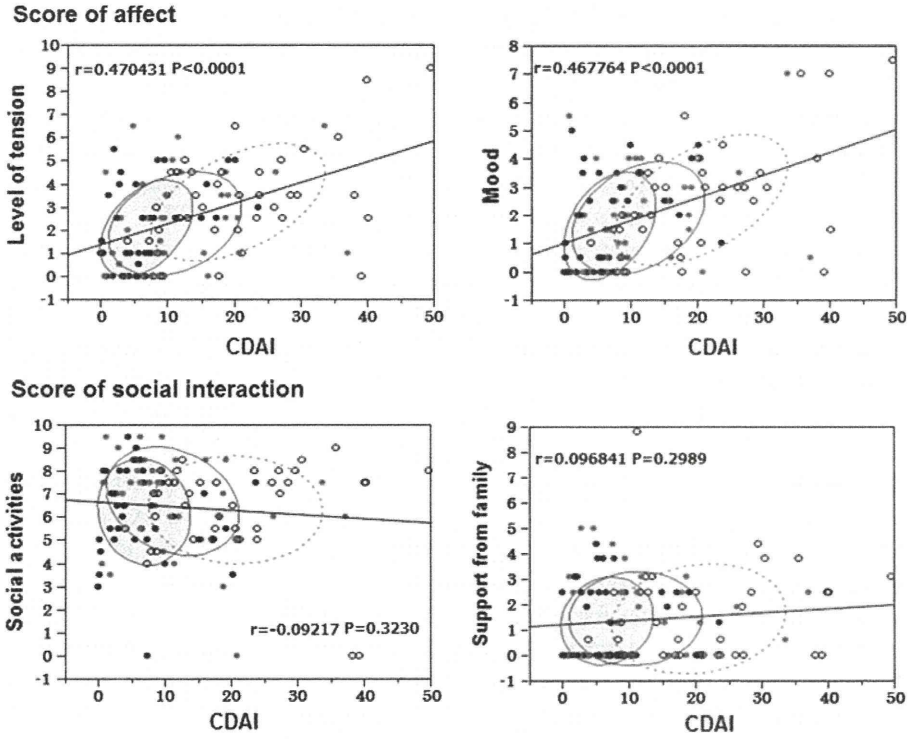
Fig. 3 Scatter plots of each item of AIMS-2 versus CDAI in patients with rheumatoid arthritis at week 4 (*open circles*), week 12 (*gray circles*) and week 24 (*closed circles*) after tocilizumab therapy. The Pearson coefficient of correlation between each item of AIMS-2 and CDAI is shown. "Symptom (pain)" 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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CASE REPORT Open Access

Tocilizumab treatment safety in rheumatoid arthritis in a patient with multiple sclerosis: a case report

Hiroe Sato[1,2*], Daisuke Kobayashi[1], Asami Abe[1], Satoshi Ito[1], Hajime Ishikawa[1], Kiyoshi Nakazono[1], Akira Murasawa[1], Takeshi Kuroda[2], Masaaki Nakano[3] and Ichiei Narita[2]

Abstract

Background: Multiple sclerosis is a relatively rare disease, and complications of multiple sclerosis and rheumatoid arthritis are much rarer. Since anti-tumor necrosis factor therapy increases exacerbations of multiple sclerosis, complications of demyelinating diseases contraindicate anti-tumor necrosis factor therapy. There have been few reports of anti-interleukin-6 receptor therapy for patients with rheumatoid arthritis complicated with multiple sclerosis.

Case presentation: A 53-year-old Japanese woman with multiple sclerosis and rheumatoid arthritis was admitted to our hospital because her rheumatoid arthritis was uncontrolled with oral methotrexate, tacrolimus, and prednisolone. She had developed multiple sclerosis when she was 25 years old and was treated with glucocorticoid therapy. Her multiple sclerosis was in remission for more than 9 years. Because anti-tumour necrosis factor therapy can exacerbate demyelinating disease, the anti-interleukin-6 receptor antibody tocilizumab was started at 8 mg/kg every 4 weeks. At the second administration of tocilizumab, complete remission was achieved. She has remained in remission with tocilizumab without recurrence of multiple sclerosis for more than 5 years.

Conclusion: Anti-interleukin-6 therapy was safely used in this patient with rheumatoid arthritis without exacerbations of multiple sclerosis.

Keywords: Rheumatoid arthritis, Multiple sclerosis, Tocilizumab, Interleukin-6, Tumour necrosis factor

Background

Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating disease of the central nervous system characterised by repeated relapses and remissions. The prevalence rate of MS in Japan is reportedly 8 to 9 per 100,000 persons. High-dose glucocorticoid therapy is used for initial and relapsed progression of MS with or without immunosuppressive agents. Although MS is an autoimmune inflammatory disease, as is rheumatoid arthritis (RA), and although the level of tumour necrosis factor (TNF) in cerebrospinal fluid is correlated with the severity and progression of the disease [1], anti-TNF therapy fails and actually increases exacerbations [2,3]. Therefore, complications of demyelinating diseases contraindicate anti-TNF therapy. There have been few reports of anti-interleukin (IL)-6 receptor therapy for patients with RA complicated with MS.

We herein describe a patient with RA and MS treated with anti-IL-6 receptor therapy.

Case presentation

A 53-year-old Japanese woman was admitted to Niigata Rheumatic Centre, Shibata city, Japan. She had been diagnosed with MS associated with right optic neuritis and thoracic myelitis when she was 25 years old and treated with high-dose prednisolone (PSL). The myelitis had relapsed three times when she was 36, 37 and 40 years old and treated with high-dose PSL. Oligoclonal

* Correspondence: hiroe-212@umin.ac.jp
[1]Department of Rheumatology, Niigata Rheumatic Center, 1-2-8 Honcho, Shibata City, Niigata 957-0054, Japan
[2]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-Dori, Chuoku, Niigata City, Niigata 951-8510, Japan
Full list of author information is available at the end of the article

IgG band was found in cerebral spinal fluid (CSF) and IgG and myelin basic protein in CSF were elevated (4.9 mg/dL and 1.2 mg/dL, respectively). Brain T2 weighted magnetic resonance imaging (MRI) showed high intensity area beside left lateral ventricle indicating asymptomatic plaque lesion due to MS. High intensity area was also shown in T2 weighted MRI of cervical spinal cord. Anti-aquaporin 4 antibody was negative. Slight right hemiparesis remained, and she needed a cane to walk outside. The MS achieved remission and PSL was stopped for 9 years. When she was 50 years old, polyarthritis developed, and rheumatoid factor and C-reactive protein (CRP) levels were high. She was diagnosed with RA. The PSL was restarted at 7.5 mg daily and methotrexate (MTX) was begun. Because the MTX could not be increased over 8 mg/week because of mild elevation of transaminases, tacrolimus (3 mg daily; TAC) was added to MTX and leukocyte apheresis was performed. However, the RA activity remained high: the CRP was 2.3 mg/dL and the disease activity score (DAS28ESR) was 4.94 (moderate disease activity). Furthermore, joint space narrowing of both knees and ankles had progressed obviously over 1 year. Because anti-TNF therapy can exacerbate demyelinating disease, the anti-IL-6 receptor antibody tocilizumab (TCZ) was started at 8 mg/kg every 4 weeks. At the second administration of TCZ, the CRP was <0.1 mg/dL and the DAS28ESR was 2.0 (complete remission). The MTX and TAC were tapered and stopped in 6 months, and the PSL was tapered to 0.5 mg daily in 1 year. The health assessment questionnaire disability index (HAQ DI) in 1 year was 1.88 and functional disability was remained. At the 5-year follow-up, she remained in remission with TCZ.

Serum interferon (IFN) -γ was negative (≤0.1 IU/mL) and serum high sensitivity TNF-α was within normal range (1.6 pg/mL) before starting TCZ therapy. Both of them kept the same levels for a year. Serum IL-6 level was elevated, 51.2 pg/mL (normal range; ≤4.0 pg/mL) before starting TCZ therapy and it was 57.1 pg/mL a year later.

Discussion

Complications of MS and RA are rare, and only a few cases have been reported [4,5]. In two case reports, the duration between the onset of each disease was long (8–20 years), and RA or MS was preceded by the other and the two diseases did not flare at the same time [4,5]. Our patient with MS also developed RA 25 years after the onset of MS, which was well controlled without medication for 9 years. Thus, the onset mechanisms of MS and RA are expected to fundamentally differ despite the fact that both are autoimmune inflammatory diseases.

On the other hand, there are several reports of patients with RA who developed demyelinating diseases during anti-TNF therapy [6-8] and patients with MS who developed inflammatory arthritis during IFN-β therapy [9,10]. The mechanisms of demyelinating disease induced by anti-TNF therapy are not clear, but inhibition of TNF leads to IFN-γ production, which is associated with MS [11]. Moreover, TNF polymorphism may be associated with anti-TNF therapy-induced demyelinating diseases [12]. IFN-β therapy for preventing recurrence of relapsing-remitting MS and secondary progressive MS is now widely used. Arthritis reportedly develops during IFN-β therapy in patients with MS, and the HLA phenotype may be involved in its pathogenesis [9]. Elevated levels of IL-6 in the serum in response to IFN-β therapy may also be associated with arthralgia [10].

In comparison, few studies have reported anti-IL-6 therapy in demyelinating disorders. A case report of a 72-year-old woman with leukoencephalopathy that developed in a Phase 3 clinical trial of TCZ for treating RA has been published [13]. However, the relationship between TCZ and leukoencephalopathy was not clear because the possibility of infection had not been completely excluded and the symptoms did not improve after discontinuing TCZ.

Studies involving mouse models of MS (experimental autoimmune encephalomyelitis, EAE) and RA (collagen-induced arthritis, CIA) have revealed that Th-17 plays an important role in the development of both diseases [14,15]. Furthermore, IL-6 mainly affects the differentiation of Th-17 in the mouse, and anti-IL-6 therapy inhibits the onset of EAE and CIA. Meanwhile, TNF affects local inflammation [14,15]. Thus, anti-IL-6 therapy may control EAE and CIA earlier and more radically than anti-TNF therapy. In humans, IL-6 mainly affects the differentiation of Th-17, as in the mouse, and anti-IL-6 therapy should theoretically inhibit both RA and MS. However, the cytokine pathways differ in humans and mice, and further studies are needed to determine whether anti-IL-6 therapy can be used safely in patients with MS.

Conclusion

Here, we reported a patient with RA complicated by MS who was treated with anti-IL-6 therapy for more than 5 years without an exacerbation of the MS. Because anti-TNF therapy can induce and worsen demyelinating diseases, anti-IL-6 therapy is a potential treatment for patients with RA complicated by MS.

Consent

Written informed consent was obtained from the patient for publication of this Case Report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations
RA: Rheumatoid arthritis; MS: Multiple sclerosis; TNF: Tumour necrosis factor; IL: Interleukin; PSL: Prednisolone; CSF: Cerebral spinal fluid; MRI: Magnetic resonance imaging; CRP: C-reactive protein; MTX: Methotrexate; TAC: Tacrolimus; TCZ: Tocilizumab; IFN: Interferon; EAE: Experimental autoimmune encephalomyelitis; CIA: Collagen-induced arthritis.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
HS, DK, AA, SI, HI, KN and AM made substantial contributions to conception and acquisition of data and analysis and interpretation of data. TK, MN and IN helped to draft the manuscript. All authors read and approved the final manuscript.

Author details
[1]Department of Rheumatology, Niigata Rheumatic Center, 1-2-8 Honcho, Shibata City, Niigata 957-0054, Japan. [2]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-Dori, Chuoku, Niigata City, Niigata 951-8510, Japan. [3]Department of Medical Technology, School of Health Sciences, Faculty of Medicine, Niigata University, 2-746 Asahimachi-Dori, Chuoku, Niigata City 951-8518, Japan.

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ORIGINAL ARTICLE

Effects of surgical intervention on disease activity of rheumatoid arthritis: Cases of surgery for rheumatoid arthritis of the lower limbs treated with biologics

Koei Oh, Hajime Ishikawa, Asami Abe, Hiroshi Otani, Kiyoshi Nakazono, and Akira Murasawa

Division of Rheumatology, Niigata Rheumatic Center, Shibata, Niigata, Japan

Abstract

Objectives. In order to verify combination therapy with drugs and surgery for rheumatoid arthritis (RA), we evaluated changes in clinical outcome affected by surgical intervention in the patient treated with biologics and investigated the effects of surgery on disease activity.
Methods. Fifty-five lower limb joint surgeries were performed in 48 patients under biological therapy. DAS28-ESR, modified Health Assessment Questionnaire (mHAQ) score, PtGA and serum CRP were examined just before surgery, at 6 months and at 12 months after surgery. A kind of suitable medication and its dose were investigated.
Results. Preoperative DAS28-ESR significantly decreased from 3.71 ± 1.19 (mean ± SD) to 3.37 ± 1.22 at 6 months and to 3.24 ± 1.05 at 12 months postoperatively. mHAQ score did not change, but, PtGA and serum CRP improved. In 43 (78.2%) patients in whom no change or decrease in medication during the follow-up period, excluding the effect of drugs, DAS28-ESR also decreased significantly from 3.53 ± 1.17 to 3.16 ± 1.16 at 6 months, and to 3.16 ± 0.98 at 12 months.
Conclusions. Lower limb surgery performed under biological therapy enhances the effects of not only improving joint function but also of ameliorating systemic disease activity.

Keywords

Biologics, Disease activity, Lower limb, Rheumatoid arthritis, Surgical intervention

History

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Introduction

With a spread of biological therapy, surgery is often performed for rheumatoid arthritis (RA) treated with biologics. It is reported that not only drug therapy but also combination therapy with drugs and surgery can achieve better therapeutic effects [1]. In this study, we evaluated changes in clinical outcome affected by surgical intervention in RA patients treated with biologics and investigated the effects of surgery on disease activity.

Subjects and methods

Of 92 surgically-treated RA patients administered biologics in Niigata Rheumatic center between April 2005 and June 2012, 48 patients who had undergone lower limb joint surgery were evaluated. There were 55 surgical procedures. On seven patients, two procedures were performed in a same individual with an interval of more than 1 year.

The patients in this study met the ACR Criteria of 1987 [2] or the 2010 ACR/EULAR RA Classification Criteria [3]. In regard to the use of biologics during the perioperative period, the patients underwent a drug washout period based on the guideline for biologics of the Japan College of Rheumatology [4].

There were 3 men and 45 women with a mean age of 61 (37–80) years and a mean disease duration of 12 (1–20) years. According to Steinbrocker's stage classification [5], 8 cases were in Stage II, 32 in Stage III and 15 in Stage IV. And according to its functional class classification, 26 cases were in Class 2, 22 in Class 3 and 7 in Class 4, respectively. Surgical procedure included 21 total knee arthroplasties (TKA), 17 toe surgeries, 8 total hip arthroplasties, 3 ankle arthrodeses and 6 knee synovectomies. The mean period between the first use of biologics and surgery was 1.6 years. Biologics used included infliximab in 25 cases; etanercept in 12, tocilizumab in 9, adalimumab in 1, and postoperative switching of biologics was done in 8 (Table 1).

The following items were examined just before surgery and at the time of 6 months and 12 months postoperatively: Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) [6], functional assessment of lower limb outcomes with

Table 1. Characteristics of the patient.

	55 surgical procedures in 48 cases
Gender	Male: 3 cases, female: 45 cases
Mean age at surgery (years)	61.2 (37–80)
Mean disease duration (years)	12.1 (1.4–20)
Stage	II: 8 cases, III: 32 cases, IV: 15 cases
Class	2:26 cases, 3:22 cases, 4:7 cases
Surgical procedure	Total hip arthroplasty: 8 cases Total knee arthroplasty: 21 cases Synovectomy of knee: 6 cases Ankle arthrodesis: 3 cases Toe arthroplasty: 17 cases
Biological agent	Infliximab: 25 cases, Etanercept: 12 cases Tocilizumab: 9 cases, Adalimumab: 1 cases Switching of biologics: 8 cases

Correspondence to: Koei Oh, Division of Orthopaedic, Showa University, Yokohama Northern Hospital, 35-1 Chigasaki-chuo, Tsuzuki-ku, Yokohama 224-8503, Japan. Tel: 045-949-7000. Fax: 045-949-7927 E-mail: cpkoei@aol.com