Normalisation of physical function by infliximab in patients with RA: factors associated with normal physical function

H. Nagasawa[1], H. Kameda[2], N. Sekiguchi[1], K. Amano[1], T. Takeuchi[1,2]

[1]Department of Rheumatology and Clinical Immunology, Saitama Medical Centre, Saitama Medical University, Kawagoe, Japan; [2]Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Faculty of Medicine, Keio University, Tokyo, Japan.

Abstract

Objectives

We conducted a two-year prospective study to identify possible factors associated with normalisation of physical function by infliximab treatment in 125 patients with rheumatoid arthritis (RA).

Methods

RA patients who had been scheduled to receive infliximab at 3 mg/kg were registered and prospectively examined for disease activity, joint damage, and physical function for 102 weeks using the Disease Activity Score of 28 Joints (DAS-28) using C-reactive protein, van der Heijde-modified Sharp score (vdH-Sharp score) of hand and foot x-ray, and Health Assessment Questionnaire Disability Index (HAQ-DI). Normal physical function and clinical remission were defined as a HAQ-DI of 0.5 or less, and DAS28 (CRP) <2.6, respectively.

Results

Forty-two of 125 patients (42%) achieved normal physical function at 102 weeks. The percentage of normal physical function at 102 weeks was significantly higher in the patients achieving clinical remission at 102 weeks (60%) than in those without (16%). In the patients with clinical remission at 102 weeks, less structural damage at baseline was correlated with a higher rate of normal physical function, suggesting the critical importance of joint destruction prior to infliximab therapy, in addition to clinical response. Logistic regression analysis further identified HAQ-DI, serum MMP-3 level, vdH-Sharp score, and methotrexate (MTX) dose as baseline factors contributing to normal physical function with 2-year infliximab treatment.

Conclusion

Treatment with anti-TNF biologics in combination with MTX may achieve the normalisation of physical function in patients with established RA. Critical factors contributing to the normalisation of function were tight control of disease activity and less joint damage.

Key words

Disease Activity Score of 28 Joints (DAS28), Health Assessment Questionnaire Disability Index (HAQ-DI), infliximab, rheumatoid arthritis, van der Heijde-modification of the Sharp score (vdH-Sharp score)

Hayato Nagasawa, MD, PhD
Hideto Kameda, MD, PhD
Naoya Sekiguchi, MD
Koichi Amano , MD, PhD
Tsutomu Takeuchi, MD, PhD

This work was supported by grants from Ministry of Health, Labour and Welfare (no. H19-Immunology-general-006).

Please address correspondence and reprint requests to:
Hayato Nagasawa MD,
Department of Rheumatology and Clinical Immunology,
Saitama Medical Centre,
Saitama Medical University,
1981 Kamoda, Kawagoe,
Saitama 350-8550, Japan.
E-mail: nagasawa@saitama-med.ac.jp

Received on October 28, 2009; accepted in revised form on January 13, 2010.

Conflict of interest: Dr Takeuchi has received consultancy fees from Mitsubishi-Tanabe Pharma, Bristol-Myers Squibb, Novartis, and and lecture fees from Mitsubishi-Tanabe Pharma, Takeda Pharmaceutical Co. Ltd., Abbott, Eisai Pharma, Chugai Pharma; Dr Kameda has received honoraria from Mitsubishi-Tanabe Pharma, Centocor, Wyeth Japan, Takeda Pharmaceutical Co. Ltd., Abbott, Eisai Pharma, Chugai Pharma, and Bristol-Myers Squibb; the other co-authors have declared no competing interests.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease that is primarily characterised by persistent and progressive synovitis, in which synovial inflammation leads to cartilage destruction, bone erosion and subsequent disability (1). Since the ultimate goal of RA treatment is to maintain normal functional capability, much attention has been paid to the temporal change in functional capability during treatment. These studies have been facilitated by methodological improvements which have allowed a detailed description of physical function in RA patients. The most widely used disease-specific instrument is the health assessment questionnaire disability Index (HAQ-DI) (2, 3) and its modified version, the modified HAQ (MHAQ) (4). Accumulating evidence now indicates that HAQ-DI predicts severe outcomes in these patients, including co-morbidity, mortality and work disability (5, 6). Functional capability in RA patients is likely affected by both disease processes, such as inflammation, and disease outcome, such as joint damage, and associations between HAQ-DI score and disease activity, joint destruction, muscle strength, psychosocial factors, age and sex have been reported (7-12).

The inflammatory cytokine tumour necrosis factor-α (TNF-α) plays a pivotal role in the pathogenesis of RA (13-15), and biological agents targeting this factor are efficacious not only in the control of synovial inflammation but also in halting structural damage, leading to the improvement and maintenance of HAQ-DI score (16-20). When joint destruction has progressed to end-stage disease, functional improvement may not be sufficient even with anti-TNF therapy. In this regard, it remains unclear whether anti-TNF biologics can provide normal physical function, particularly in patients with advanced disease, and if so, what factors are associated with normal physical function.

In this study, we prospectively enrolled One hundred and twenty-five RA patients who had been scheduled to receive infliximab in a single academic center, and evaluated disease activity, structural damage, and physical function for two years during infliximab treatment. We also attempted to identify factors possibly associated with normal physical function (HAQ-DI ≤0.5) at 102 weeks in these patients.

Patients and methods

Study design and patients

The study was conducted under a prospective longitudinal cohort design. RA patients who fulfilled the 1987 revised criteria of the American College of Rheumatology (ACR) (21) for the classification of RA, satisfied the Japanese guideline for the use of anti-TNF biologics (22), and intended to receive infliximab were invited to participate between September 2003 and March 2006. Written informed consent was obtained from 125 patients (15 men and 110 women), who were enrolled in the study.

Treatment

Patients were scheduled to receive infliximab at a dose of 3 mg/kg at weeks 0, 2, 6 and subsequently every 8 weeks thereafter. If a patient did not show a sufficient response to infliximab therapy, the dosage was increased up to a maximum of 200 mg/patient for patients with a body weight of less than 67 kg, the interval of infusion was shortened by up to 6 weeks, or both. These dose-intensifying therapeutic modifications were performed in 55% of patients. Infliximab was continued throughout 2 years in 93 patients, while 32 patients discontinued infliximab because of complete remission in 14, adverse events in 4, lack of efficacy in 13, and other reasons in 2 patients, respectively.

Assessment

Patients were followed-up longitudinally by examination at each infusion visit over 102 weeks. To monitor parameters of disease activity, serum levels of C-reactive protein (CRP), matrix metalloproteinase-3 (MMP-3), and the Disease Activity Score of 28 joints (DAS28)-CRP scores were determined at each visit (23). We defined clinical remission as DAS28 (CRP) <2.6 (24). Functional status was assessed with the health assessment questionnaire disability index (HAQ-DI), and normal physical func-

tion was defined as a HAQ-DI score ≤0.5 (2, 24, 25).

Hand and foot x-rays were obtained at 0, 54, and 102 weeks. Articular damage and progression were scored according to the van der Heijde-modification of the Sharp score (vdH-Sharp score) by two expert readers who were blinded to the patient's identity but had knowledge of the chronological order of the films. Radiographic progression was judged using two methods: progression >0.5 and progression > the smallest detectable difference (SDD) (26). The SDD for the mean change from baseline using two readers' scores for each patient's radiographs was 4.39 (standard deviation of per-patient differences between the readers divided by the square root of 2), which corresponds to nearly 1% of the maximum vdH-Sharp score of 448.

Statistical analysis

The statistical analysis was performed using the JMP software, version 8.01 (SAS Institute, Cary, North Carolina, USA). Spearman correlation analyses were performed between HAQ-DI score as a dependent variable and clinical measures as explanatory variables at baseline. Clinical measures were analyzed by the Wilcoxon test for nonparametric comparisons between groups for continuous variables. For categorical response variables, patient group comparisons were made using the χ^2 test. Missing variables in clinical measures other than radiographic scores at 54 and 102 week were imputed using the last-observation carried forward method. In the statistical model which explored factors associated with normal physical function at week 102, logistic regression analysis was used to adjust for the confounding effect of correlated variables. In this model, patients were classified into two groups based on HAQ score at 102 w: HAQ ≤0.5 (normal physical function) and HAQ >0.5. This value was chosen based on a mean normal population-based score for HAQ-DI of 0.5 or less (24, 25). Odds ratio (OR) and confidence intervals for normal physical function were estimated, and differences were considered significant at a *p*-value <0.05.

Tab. I. Baseline characteristics of the patients.

Demographics	Age (years)	52.8 ± 13.3 (19-83)*
	female (%)	110 (88)**
Clinical characteristics	Duration (years)	7.9 ± 6.9 (0.3-30.8)*
	0 < ≤ 2	25 (20.0)**
	2 < ≤ 5	29 (23.2)**
	5 < ≤ 10	33 (26.4)**
	10 <	38 (30.4)**
	DAS28 (CRP)	5.4 ± 1.2 (2.54-7.89)*
	CRP (mg/dl)	3.4 ± 3.0 (0-13.6)*
	MMP-3 (ng/ml)	322.5 ± 297.8 (0-1460)*
	HAQ-DI	1.4 ± 0.7 (0-3)*
	RF positive	104 (83)**
	MTX (mg/w)	8.6 ± 2.7 (4-20)*
	prednisolone treatment (%)	91 (72.8)**
	prednisolone dosage (mg/day)	5.9 ± 2.8 (1-15)*
Radiographic findings	modified vdH-Sharp	116.2 ± 96.7 (0-404)*
	estimated yearly progression	12.0 ± 17.7 (0-80.4)*

*mean ± standard deviation (range); **number (%) of patients; DAS 28: Disease Activity Score of 28 joints; CRP: C-reactive protein; MMP-3: matrix metalloproteinase-3; HAQ-DI: Health Assessment Questionnaire Disability Index; RF: Rheumatoid factor; MTX: methotrexate; vdH-Sharp score: the van der Heijde modification of the Sharp score.

Results

Baseline characteristics of patients and correlation with HAQ-DI score

As shown in Table I, baseline characteristics of the patients included the mean age of 52.8 (range: 19-83) and the mean disease duration of 7.9 years (range: 0.3–30.8). The mean DAS28 (CRP) was 5.4 and the mean HAQ-DI was 1.4. Rheumatoid factor (RF) was positive in the sera of 104 patients (83%). Ninety-one patients (73%) were receiving corticosteroids (5.9±2.8 mg/day prednisolone equivalent, range: 1–15 mg/day) at the time of study entry. Mean MTX dose was 8.6 mg/week (range: 4-20 mg/week). In addition, the mean vdH-Sharp score at baseline was 116.2 with the mean estimated yearly progression of 12.0. These results indicate that the patients had advanced RA with high disease activity and moderate to severe disability.

To clarify patients characteristics related to disability before infliximab treatment, we analysed possible correlations between a series of clinical measures and HAQ-DI score at baseline (Table II). No significant correlation with HAQ-DI score was seen for age, disease duration, RF titer, CRP, MMP-3, MTX dose, vdH-Sharp score, or estimated yearly progression of vdH-Sharp score, whereas a significant correlation was seen for baseline DAS28 (CRP) (r=0.53, $p<0.0001$), suggesting that the major contributor to disability before treatment with anti-TNF biologics in these patients was disease activity, rather than joint damage.

Change in DAS28 (CRP) and HAQ-DI during treatment

Since disease activity was the main factor contributing to disability at baseline, we examined disease activity and disability in RA patients during treatment with infliximab. As shown in Fig. 1a, The mean DAS28 (CRP) levels decreased rapidly at 2 weeks after the start of infliximab and reached a near-plateau level by 30 weeks (from 5.4 at baseline to 3.5 at 2 w, 3.0 at 30 w, 2.8 at 54 w, and 2.8 at 102 w). Among patients, clinical

Table II. Correlation between baseline HAQ-DI score and baseline clinical measures.

Age (years)	0.16	0.1883
Disease duration (years)	0.21	0.8932
RF titer (IU/ml)	0.19	0.2075
DAS28 (CRP)	0.53	<1.0001
CRP (mg/dl)	0.33	0.2358
MMP-3 (ng/ml)	0.08	0.4021
MTX dose (mgf/week)	-0.14	0.3978
vdH-Sharp score	0.30	0.5354
Estimated yearly progression of vdH-Sharp score	0.20	0.2059

RF: Rheumatoid factor; DAS 28: Disease Activity Score of 28 joints; CRP: C-reactive protein; MMP-3: matrix metalloproteinase-3; MTX: methotrexate; vdH-Sharp score: the van der Heijde modification of the Sharp score.

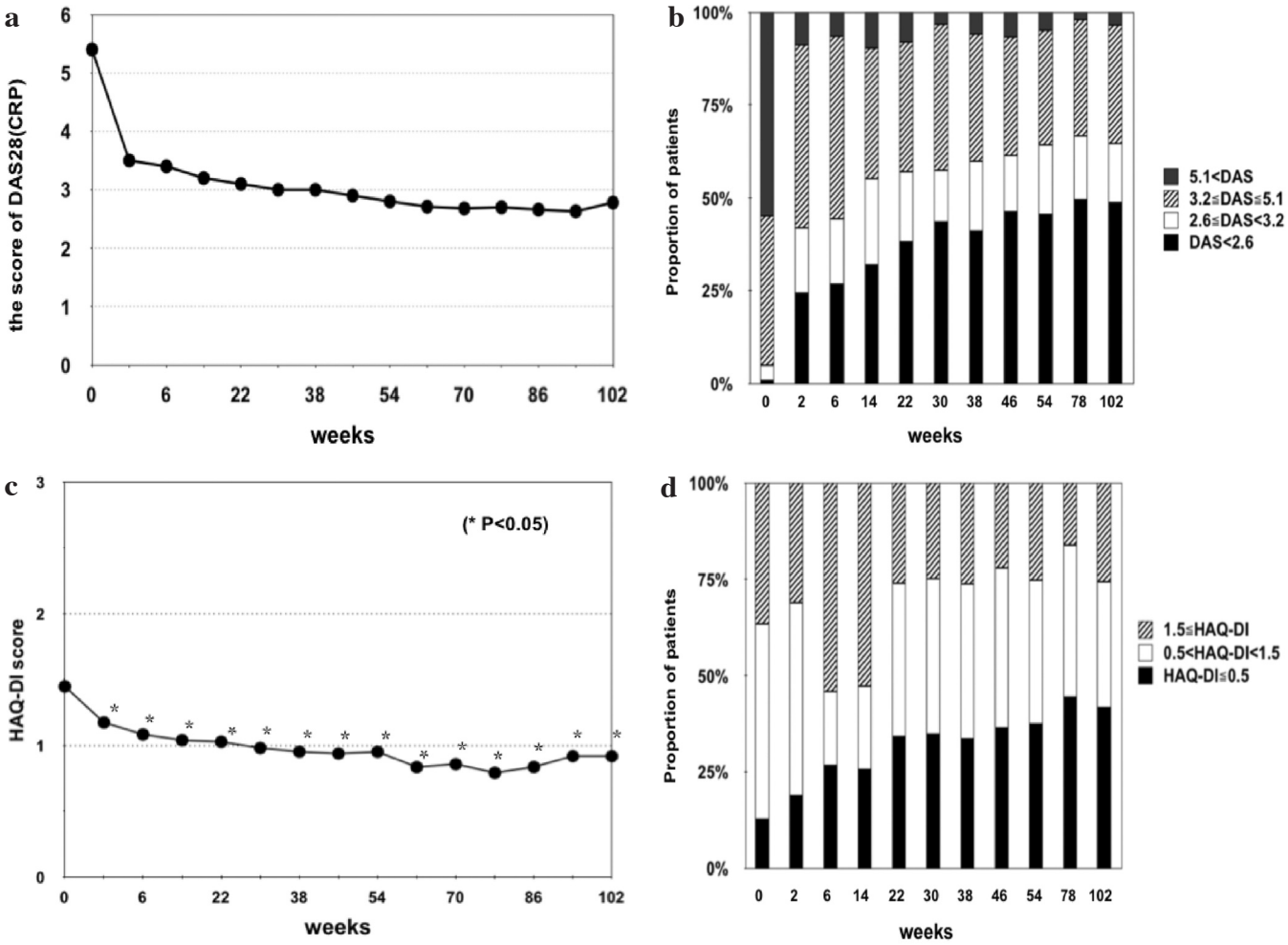

Fig. 1a. Mean change in DAS28-CRP with infliximab from baseline to 102 weeks in 125 patients.
b. Categorical change in disease activity with infliximab. The *solid area* represents the percentage of cases in clinical remission, the *open area* the percentage with low activity, the *hatched area* the percentage with moderate activity, and the *half solid area* the percentage with high disease activity.
c. Mean change in HAQ-DI with infliximab from baseline to 102 weeks in 125 patients. HAQ-DI scores were obtained at each visit in all patients. *p<0.05 vs the value at baseline.
d. Categorical change in HAQ-DI with infliximab. The *solid area* represents the percentage of cases achieving functional remission (HAQ-DI≤0.5), the *open area* the percentage with low or moderate functional disability (0.5<HAQ-DI<1.5), and the *hatched area* the percentage with severe functional disability (1.5≤HAQ-DI).

remission was reached by 0.8%, 43.4%, 45.5%, and 48.7% at baseline, 30, 54, and 102 weeks, respectively, whereas disease activity remained in 32% at 102 weeks (Fig. 1b).

Similarly, the mean HAQ-DI score decreased as early as 2 weeks after the start of infliximab and nearly stabilised by 30 weeks (mean HAQ-DI score: from 1.4 to 1.2 at 2 w, 1.0 at 30 w, 1.0 at 54 w, and 0.9 at 102 w) (Fig. 1c). Among patients, normal physical function was achieved by 12.9%, 34.7%, 37.4%, and 41.6% at baseline, 30, 54, and 102 weeks. In contrast, the proportion with severe functional disability (HAQ-DI≧1.5) gave a reduction by only 11% from 37% to 26% (Fig. 1d).

Clinical characteristics of patients with normal physical function following infliximab treatment for 102 weeks

To explore possible factors associated with normal physical function with infliximab treatment at 102 weeks, we compared clinical variables in patients with and without normal physical function at 102 weeks (Table III). Compared to those with HAQ-DI >0.5, patients with HAQ-DI ≤0.5 at 102 weeks showed significantly shorter disease duration (5.5±5.7 *vs*. 9.6±7.1 years, p=0.0003), significantly lower baseline DAS (CRP) and lower mean DAS (CRP) during 2 years (baseline: 5.1±1.1 *vs*. 5.6±1.2, p=0.0137; mean: 2.4±0.6 *vs*. 3.2±0.7, p<0.0001), significantly higher baseline MMP-3 (371.3±321.8 *vs*. 285.2±274.7 ng/ml, p=0.0436), significantly lower baseline HAQ-DI score and mean HAQ-DI score during 2 years (baseline: 1.1±0.7 *vs*. 1.7±0.6, p<0.001; mean: 0.4±0.7 *vs*. 1.3±0.5, p<0.001), significantly higher baseline MTX dose (9.4±3.0 vs. 8.0±2.3 mg/w, p=0.0072), and significantly lower baseline vdH-Sharp score (70.4±53.5 *vs*. 150.2±107.3, p<0.0001). In contrast, no significant difference between groups was seen in estimated yearly progression before treatment and yearly progression after treatment (Table III). Overall, these results suggest that the primary determinant of normal

Tab. III. Clinical measures in patients with or without normal physical function at 102 week*.

Clinical measures	normal physical function at 102w (HAQ-DI < 0.5		*p*-value
	(+) n=52	(-) n=73	
Disease duration (years)	5.5 ± 5.7	9.6 ± 7.1	*p*=0.0003
DAS28 (CRP) at baseline	5.1 ± 1.1	5.6 ± 1.2	*p*=0.0137
MMP-3 at baseline (ng/ml)	371.3 ± 321.8	285.2 ± 274.7	*p*=0.0436
HAQ-DI at baseline	1.1 ± 0.7	1.7 ± 0.6	*p*=0.0001
mean DAS28 (CRP) (0-102w)	2.4 ± 0.6	3.2 ± 0.7	*p*=0.0001
mean HAQ-DI (0-102w)	0.4 ± 0.7	1.3 ± 0.5	*p*=0.0001
MTX (mg/w)	9.4 ± 3.0	8.0 ± 2.3	*p*=0.0072
vdH-Sharp score at baseline	70.4 ± 53.5	150.2 ± 107.3	*p*<0.0001
estimated yearly progression at baseline	24.0 ± 36.7	21.3 ± 21.3	N.S.
yearly progression during 2-year treatment	1.5 ± 2.6	1.8 ± 4.3	N.S.

*values are mean ± standard deviation; DAS 28: Disease Activity Score of 28 joints; CRP: C-reactive protein; MMP-3: matrix metalloproteinase-3; HAQ-DI: Health Assessment Questionnaire Disability Index; MTX: methotrexate; vdH-Sharp score: the van der Heijde modification of the Sharp score.

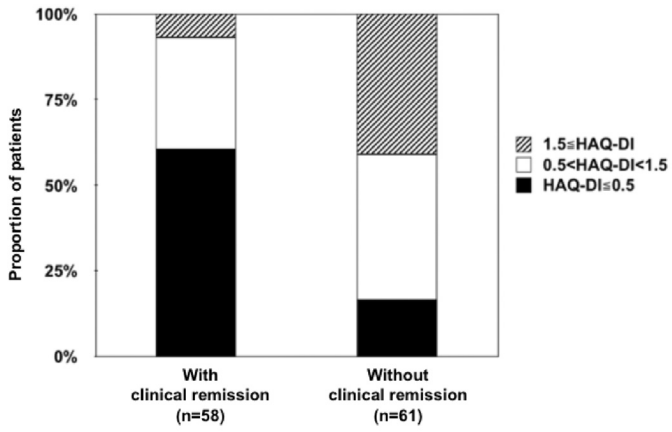

Fig. 2. Proportion of cases by HAQ-DI status with and without clinical remission. The *solid area* represents the percentage of cases with functional remission (HAQ-DI≤0.5), the *open area* the percentage with low or moderate functional disability (0.5<HAQ-DI<1.5), and the *hatched area* the percentage with severe functional disability (1.5≤HAQ-DI).

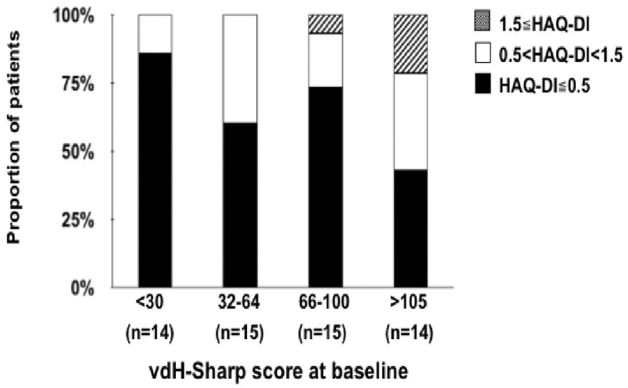

Fig. 3. Relationship between vdH-Sharp score at baseline and HAQ-DI status in 58 patients with clinical remission at 102 weeks. The *solid area* represents the percentage of cases with functional remission (HAQ-DI≤0.5), the *open area* the percentage with low or moderate functional disability (0.5<HAQ-DI<1.5), and *the hatched area* the percentage with severe functional disability (1.5≤HAQ-DI).

physical function at 102 weeks was infliximab's control of disease activity. Of note, baseline vdH-Sharp score was significantly lower and disease duration was significantly shorter in patients achieving normal physical function, raising the possibility that joint damage at baseline may have a role in better functional outcome 2 years later.

HAQ-DI status by clinical remission status at 102 weeks

Since disease activity was primarily responsible for disability in these patients before treatment, we examined physical functional status in those with and without clinical remission at 102 weeks by infliximab treatment. As shown in Fig. 2, the percentage of patients with normal physical function at 102 weeks was significantly higher among those achieving clinical remission at 102 weeks (60%) than in those without remission (16%). As shown in figure 1d, only 13% of patients had normal physical function and 37% of patients had a HAQ-DI greater than 1.5 before infliximab treatment, indicating a marked improvement in physical functional status in patients with clinical remission at 102 weeks, while those without clinical remission showed no such improvement. Conversely, the proportion of patients with clinical remission was higher in patients with normal physical function at 102 weeks than in those without (73% *vs*. 27%, data not shown), indicating that control of disease activity in patients treated with infliximab was closely associated with improvement in physical functional status.

Relationship of baseline vdH-Sharp score with HAQ status at 102 weeks in patients with clinical remission

To further clarify the role of baseline joint damage in achieving normal physical function at 102 weeks, we classified the 58 patients with clinical remission at 102 weeks into 4 groups by quartile of vdH-Sharp score at baseline (Fig. 3). Results showed that the percentage of patients with normal physical function at 102 weeks was dependent on baseline vdH-Sharp score, at 85.7% in the lowest quartile group (<30 units) versus 42.9% in the highest (>105 units), indicating an inverse association between the achievement of normal physical function and the baseline degree of joint damage.

Logistic regression analysis for normal physical function at 102 weeks

To account for confounding factors among clinical variables at baseline, we finally examined the association between baseline clinical measures and normal physical function at 102 weeks by logistic regression analysis (Table IV). Results showed that normal physical function was associated with a lower baseline HAQ (per 0.1 score; OR 2.60E-08, *p*<0.01), higher base-

Tab. IV. Clinical variables associated with normal physical functional at 102w by logistic regression analysis.

Clinical measures	Adjusted odds ratio	95% CI	*p*-value
Male	1.14	0.24 – 5.63	0.8691
Age (years)	0.99	0.96 – 1.01	0.7149
Duration (years)	1.00	0.94 – 1.00	0.6443
RF (IU/ml, per 100 unit)	1.00	0.99 – 1.00	0.4767
DAS28 (CRP) at baseline (per score)	0.92	0.51 – 1.68	0.7856
CRP at baseline (mg/dl, per unit)	0.99	0.80 – 1.24	0.9575
MMP-3 at baseline (ng/ml, per 100 unit)	1.27	1.05 – 1.57	0.0019*
HAQ-DI at baseline (per 0.1 score)	2.60E-08	5.9E-13 – 0.0003	0.0001*
vdH-Sharp score at baseline (per 10 score)	0.84	0.76 – 0.93	0.0084*
MTX (per mg/w)	1.28	1.05 – 1.60	0.0142*

RF: Rheumatoid factor; DAS 28: Disease Activity Score of 28 joints; CRP: C-reactive protein; MMP-3: matrix metalloproteinase-3; HAQ-DI: Health Assessment Questionnaire Disability Index; vdH-Sharp score: the van der Heijde modification of the Sharp score; MTX: methotrexate.

line MMP-3 (per 100 units; OR 1.27, $p<0.01$), lower baseline vdH-Sharp score (per 10 score; OR 0.84, $p<0.01$), and higher baseline MTX dose (per mg/w; OR 1.28, $p=0.01$). Gender, age, disease duration, RF, DAS, and CRP at baseline were not associated with normal physical function. The above results suggest that both the tight control of disease activity by treatment and baseline joint damage notably contribute to the achievement of normal physical function with infliximab treatment for 2 years.

Discussion

In this study, we showed that infliximab treatment in a daily clinical practice setting allowed the normalisation of physical function in approximately one-third of patients with established RA. Logistic regression analysis identified HAQ-DI score, vdH-Sharp score, serum MMP-3, and MTX dose at baseline, as contributing to normal physical function at 102 weeks.

Functional disability in RA patients is generally evaluated using the HAQ-DI score, the most widely used functional outcome measure, although it is influenced by a variety of demographic factors, as well as by pain and psychological status (27-33). Recently, other measures for functional disability have been evaluated, such as loss of working time (34). In addition, clinical trials have aimed at comparing therapeutic strategies in early RA to achieve clinical remission, and even normal functional status. Although normal functional status is difficult to determine, the Outcome Measure in Rheumatology Clinical Trials (OMERACT) group has proposed preliminary definitions of minimal disease activity (MDA), including a HAQ-DI score ≤0.5 (35,36). In addition, the upper limit of 95% confidence intervals of the mean normal population-based score for HAQ-DI is 0.5 (24, 25). Accordingly, we used a cut-off 0.5 or less to indicate normal physical function. In fact, 28 patients (22.4%) achieved a HAQ-DI score of 0 at 102 weeks, which indicates ideal, or in other words normal function by this measure.

Disability in RA patients is largely affected by joint inflammation and damage. While inflammation appears to account for the early phase of the disease, joint damage gradually worsens over the entire course of the disease, resulting in apparent disability in the later phase (7-9, 37). Importantly, joint inflammation is ultimately reversible, while joint damage is not. For example, the HAQ-DI is reportedly associated with the pain score and joint tenderness, rather than joint erosion or deformity, at a given time point (38), whereas other reports have shown that the baseline radiographic score is significantly correlated with the HAQ-DI score at baseline (39) and that this correlation strengthens as disease duration lengthens (40-42). In our previous study, we also reported that patients with shorter disease duration or lower vdH-Sharp score were had a better functional status (11). Moreover, it has been shown that the reversibility of HAQ scores decreased when the duration of RA lengthened, while radiographic destruction was more advanced in a meta-analysis (43, 44). The duration of disease in this study ranged widely, allowing us to test the above hypothesis in a daily clinical practice setting. Results showed that the baseline radiographic score was significantly and independently associated with normal physical function. In contrast, disease duration, and yearly progression of vdH-Sharp score before infliximab treatment were not significantly associated with normal physical function on logistic regression analysis. Importantly, not only disease duration but also yearly progression of joint destruction before infliximab treatment were not identified as independent factors contributing to normal physical function at 102 weeks. Since baseline vdH-Sharp score represents cumulative joint damage, and estimated yearly progression is determined by the score/disease duration, these results may suggest that cumulative damage itself is important to the return of normal physical function, whereas the speed of destruction before anti-TNF treatment is not.

We also showed that baseline MTX dose was higher in patients with normal physical function at 102 weeks than in those without (9.4 *vs.* 8.0 mg/w). Logistic regression analysis showed that baseline MTX dose (pre 1 mg/w) confers an adjusted odds ratio 1.28, suggesting that MTX dose escalation should be considered before starting infliximab. These results support the conclusion of a meta-analysis of MTX therapy in RA (45). Interestingly, the adjusted odds ratio of higher MMP-3 level (per 100 U/ml) was 1.27. MMP-3 plays a key role in joint destruction, since it not only degrades matrix proteins but also activates other pro-MMPs into their active forms. The expression of MMP-3 in synovial cells is regulated by several extracellular signals including inflammatory cytokines, such as TNF-α and IL-1. In fact, Klimiuk *et al*. reported that infliximab combined with MTX resulted in rapid clinical improvement and reduced serum MMP concentrations in patients with RA (46), as we have also demonstrated (11). Further investigation is

required to confirm whether higher levels of serum MMP-3 at baseline in RA patients predict better clinical response and normal physical function by infliximab. Some previous studies showed that women and men have differences in DAS and HAQ-DI score (7, 47, 48). Then we also examined the correlation between baseline HAQ-DI score and baseline clinical measures, and the logistic regression analysis for normal physical function at 102 weeks on only female patients. These results were concordance with the whole patients (data not shown).

Several limitations of the study warrant mention. First, although the study was observational and open-labeled, and not intended to compare therapeutic strategies, the question of whether attending physicians can bias the results is valid. Nevertheless, functional status was determined using a self-reported health assessment questionnaire and statistical analysis was conducted by an independent researcher, allowing us to estimate functional status by infliximab treatment in practice conditions. Second, the study was carried out in single academic center which serves as a core regional rheumatology center for more severe and complicated patients than those treated at average rheumatology clinics. In addition, patients were selected using the guideline criteria for the use of anti-TNF biological agents proposed by the Japan College of Rheumatology, which defines indications for infliximab as including at least six swollen joint counts, six tender joints counts, and CRP ≧2mg/dl or ESR ≧28mm/h in those with an inadequate response to MTX at enrollment. Thus, most patients enrolled in this study had high disease activity. Third, owing to Japanese regulatory restrictions which limit the maximum allowable dose of MTX to 8 mg/week, MTX dosages in Japan are lower than in other countries, including the US, many European countries and even other Asian countries. Nevertheless, higher starting doses of MTX are sometimes used in daily clinical practice in Japan (49). Indeed, the mean MTX dose in the present study was 8.7 mg/week, and 30% of patients received doses greater than 8 mg/week. Recent randomised controlled trials which directly compared different dosages of oral MTX in RA showed dose-dependent efficacy, albeit with slightly greater toxicity, and higher starting doses and rapid dose escalation are now recommended (45). Nevertheless, maximum doses of MTX in daily clinical practice appear to be lower than that used in the recent clinical trials for infliximab, such as 20–25mg/week (17, 18), even in western countries (50).

In conclusion, the present study demonstrated the importance of the tight control of disease activity with anti-TNF treatment before irreversible joint destruction progresses beyond a threshold.

Reference

1. LIPSKY PE: Rheumatoid arthritis. *In*: BRAUNWALD E, FAUCI AS, KASPER DL, HAUSER SL, LONGO DL, JAMESON JL, editors. *Harrison's Principles of Internal Medicine*.15th ed: McGraw-Hill; 2001: 1928-37.
2. FRIES JF, SPITZ P, KRAINES RG, HOLMAN HR: Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23: 137-45.
3. BRUCE B, FRIES JF: The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol* 2003; 30: 167-78.
4. PINCUS T, SUMMEY JA, SORACI SA, WALLSTON KA, HUMMON NP: Assessment of patient satisfaction in activities of daily living using a modified Stanford health assessment questionnaire. *Arthritis Rheum* 1983; 26: 1346-53.
5. PINCUS T, SOKKA T: Quantitative target values of predictors mortality in rheumatoid arthritis as possible goals for therapeutic interventions: an alternative approach to remission or ACR20 responses? *J Rheumatol* 2001; 28: 1723-34.
6. SOKKA T, PINCUS T: Markers for work disability in rheumatoid arthritis. *J Rheumatol* 2001; 28: 1718-22.
7. WELSING PMJ, VAN GESTEL AM, SWINKEL HL, KIEMENCY LALM, VAN RIEL PLCM: The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum* 2001; 44: 2009-17.
8. DROSSAERS-BAKKER KW, DE BUCK M, VAN ZEBEN D, ZWINDERMAN AH, BREEDVELD FC, HAZES JMW: Long-term course and outcome of functional capacity in rheumatoid arthritis. *Arthritis Rheum* 1999; 42: 1854-60.
9. SCOTT DL, PUGNER K, KAARELA K *et al*.: The links between joint damage and disability in rheumatoid arthritis. *Rheumatology* 2000; 39: 122-32.
10. GUILLEMIN F, BRIANCON S, POUREL J: Functional disability in rheumatoid arthritis: two different models in early and established disease. *J Rheumatol* 1992; 19: 366-9.
11. NAGASAWA H, KAMEDA H, SEKIGUCHI N, AMANO K, TAKEUCHI T: Improvement of the HAQ score by infliximab treatment in patients with RA: its association with disease activity and joint destruction. *Mod Rheumatol* 2009; 19: 166-72.
12. SALAFFI F, CIMMINO MA, LEARDINI G, GASPARINI S, GRASSI W: Disease activity assessment of rheumatoid arthritis in daily practice: validity, internal consistency, reliability and congruency of the Disease Activity Score including 28 joints (DAS28) compared with the Clinical Disease Activity Index (CDAI). *Clin Exp Rheumatol* 2009; 27: 552-9.
13. FELDMANN M, BRENNAN FM, MAINI RN: Role of cytokines in rheumatoid arthritis. *Annu Rev Immunol* 1996; 14: 397-440.
14. IVASHKIV LB: Cytokine expression and cell activation in inflammatory arthritis. *Adv Immunol* 1996; 63: 337-76.
15. CHOY EH, PANAYI GS: Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med* 2001; 344: 907-16.
16. BREEDVELD FC, EMERY P, KEYSTONE E *et al*.: Infliximab in active early rheumatoid arthritis. *Ann Rheum Dis* 2004; 63: 149-55.
17. ST CLAIR EW, VAN DER HEIJDE DM, SMOLEN JS *et al*.: Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004; 50: 3432-43.
18. GOEKOOP-RUITERMAN YPM, DE VRIES-BOUWSTRA JK, ALLAART CF *et al*.: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum* 2004; 52: 3381-90.
19. QUINN MA, CONAGHAN PG, O'CONNOR PJ *et al*.: Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 27-35.
20. VIRKKI LM, KONTTINEN YT, PELTOMAA R *et al*.: Cost-effectiveness of infliximab in the treatment of rheumatoid arthritis in clinical practice. *Clin Exp Rheumatol* 2008; 26: 1059-66.
21. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
22. KOIKE R, TAKEUCHI T, EGUCHI K, MIYASAKA N; JAPAN COLLEGE OF RHEUMATOLOGY: Update on the Japanese guidelines for the use of infliximab and etanercept in rheumatoid arthritis. *Mod Rheumatol* 2007; 17: 451-8.
23. PREVOO ML, VAN'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LB, VAN RIEL PL: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
24. HUBERT HB, BLOCH DA, FRIES JF: Risk factors for physical disability in an aging cohort: the NHANES I epidemiologic follow-up study. *J Rheumatol* 1993; 20: 480-8.

25. BRUCE B, FRIES JF: The Stanford Health Assessment Questionnaire: dimensions of practical applications. *Health Qual Life Outcomes* 2003; 1: 20.
26. VAN DER HEIJDE D, LASSERE M, EDMONDS J, KIRWAN J, STRAND V, BOERS M: Minimal clinically important difference in plain films in RA: group discussions, conclusions, and recommendations OMERACT Imaging Task Force. *J Rheumatol* 2001; 28: 914-7.
27. PEASE CT, BHAKTA BB, DEVLIN J, EMERY P: Does the age of onset of rheumatoid arthritis influence phenotype? A prospective study of outcome and prognostic factors. *Rheumatology* (Oxford) 1999; 38: 228-34.
28. VLIET VLIELAND TP, BUITENHUIS NA, VAN ZEBEN D, VANDENBROUCKE JP, BREEDVELD FC, HAZES JM: Sociodemographic factors and the outcome of rheumatoid arthritis in young women. *Ann Rheum Dis* 1994; 53: 803-6.
29. WARD MM, LEIGH JP: The relative importance of pain and functional disability to patients with rheumatoid arthritis. *J Rheumatol* 1993; 20: 1494-9.
30. WOLFE F, HAWLEY DJ, WILSON K: The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996; 23: 1407-17.
31. WOLFE F, HAWLEY DJ: The relationship between clinical activity and depression in rheumatoid arthritis. *J Rheumatol* 1993; 20: 2032-7.
32. ABDEL-NASSER AM, EL-AZIM S, TAAL E, EL-BADAWY SA, RASKER JJ, VALKENBURG HA: Depression and depressive symptoms in rheumatoid arthritis patients: an analysis of their occurrence and determinants. *Br J Rheumatol* 1998; 37: 391-7.
33. UUTELA T, HANNONEN P, KAUTIAINEN H, HAKALA M, PAANANEN ML, HÄKKINEN A: Positive treatment response improves the health-related quality of life of patients with early rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 108-11.
34. ALLAIRE S, WOLFE F, NIU J, ZHANG Y, ZHANG B, LAVALLEY M: Evaluation of the effect of anti-tumor necrosis factor agent use on rheumatoid arthritis work disability: the jury is still out. *Arthritis Rheum* 2008; 59: 1082-9.
35. WELLS GA, BOERS M, SHEA B *et al*.: Minimal disease activity for rheumatoid arthritis: a preliminary definition. *J Rheumatol* 2005 Oct; 32: 2016-24.
36. KHANNA D, OH M, FURST DE *et al*.; WESTERN CONSORTIUM OF PRACTICING RHEUMATOLOGISTS: Evaluation of the preliminary definitions of minimal disease activity and remission in an early seropositive rheumatoid arthritis cohort. *Arthritis Rheum* 2007; 57: 440-7.
37. WOLFE F: A reappraisal of HAQ disability in rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 2751-61.
38. SOKKA T, KANKAINEN A, HANNONEN P: Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores. *Arthritis Rheum* 2000; 43: 386-9.
39. BREEDVELD FC, HAN C, BALA M *et al*.: Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis. *Ann Rheum Dis* 2005; 64: 52-5.
40. CLARKE AE, ST-PIERRE Y, JOSEPH L, PENROD JT, SIBLEY MH, GENANT HK: Radiographic damage in rheumatoid arthritis correlates with functional disability but not direct medical costs. *J Rheumatol* 2001; 28: 2416-24.
41. KEYSTONE EC, KAVANAUGH AF, SHARP JT *et al*.: Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004; 50: 1400-11.
42. BREEDVELD FC, WEISMAN MH, KAVANAUGH AF *et al*.: The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006; 54: 26-37.
43. ALETAHA D, SMOLEN J, WARD MM: Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. *Arthritis Rheum* 2006; 54: 2784-92.
44. SMOLEN JS, ALETAHA D, GRISAR JC, STAMM TA and SHARP JT: arthritis clinical trialsdamage-related physical disability in rheumatoid Estimation of a numerical value for joint. *Ann Rheum Dis* 2009 Epub 27 Aug.
45. RAMOS-REMUS, VALENTINI G, ZOCHLING J, DOUGADOS MIELANTS M *et al*.: Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; 68; 1086-93.
46. KLIMIUK PA, SIERAKOWSKI S, DOMYSLAWSKA I, CHWIECKO J: Effect of repeated infliximab therapy on serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in patients with rheumatoid arthritis. *J Rheumatol* 2004; 31: 238-4.
47. HYRICH KL, WATSON KD, SILMAN AJ, SYMMONS DP: Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* (Oxford). 2006; 45: 1558-65.
48. MANCARELLA L, BOBBIO-PALLAVICINI F, CECCARELLI F *et al*.: Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. *J Rheumatol* 2007; 341670-3.
49. KAMEDA H, SEKIGUCHI N, NAGASAWA H *et al*.: Development and validation of handy rheumatoid activity score with 38 joints (HRAS38) in rheumatoid arthritis patients receiving infliximab. *Mod Rheumatol* 2006; 16: 381-8.
50. SARAUX A, DEVAUCHELLE-PENSEC V, ENGERRAN L, FLIPO RM: Most rheumatologists are conservative in active rheumatoid arthritis despite methotrexate therapy: results of the PRISME survey. *J Rheumatol* 2006; 33: 1258-65.