Mod Rheumatol (2006) 16:381–388
DOI 10.1007/s10165-006-0528-9

ORIGINAL ARTICLE

**Hideto Kameda · Naoya Sekiguchi · Hayato Nagasawa
Koichi Amano · Hirofumi Takei · Katsuya Suzuki
Eiko Nishi · Hiroe Ogawa · Tsutomu Takeuchi**

Development and validation of handy rheumatoid activity score with 38 joints (HRAS38) in rheumatoid arthritis patients receiving infliximab

Received: August 29, 2006 / Accepted: September 14, 2006

Abstract The parameters involved in the Disease Activity Score of 28 joints (DAS28) are not mutually independent, and the evaluation excludes ankle and foot joints. We developed a new quantitative and comprehensive assessment of the activity of rheumatoid arthritis (RA), called the handy rheumatoid activity score, with 38 joints (HRAS38), to overcome these disadvantages of DAS28. Forty-six RA patients who recently completed a 1-year infliximab therapy were evaluated for DAS28 (C-reactive protein; CRP) and HRAS38 at 0, 2, 6, 14, 22, 30, 38, 46, and 54 weeks. The 38-joint evaluation in HRAS38 includes 28 joints of DAS28 except for the shoulder joints, with the addition of ankle and metatarsophalangeal joints. The extent of joint swelling was rated on a scale of 0–3. The HRAS38 score is the cumulative sum of three parameters including: (1) a global assessment of disease activity [visual analog scale (VAS) 0–100 mm] by the patient, (2) swollen joint score based on a 38-joint assessment by a physician (0–114), and (3) serum concentration of CRP (mg/l). Scatter plots of HRAS38 and DAS28(CRP), and subsequent linear regression analysis demonstrated a statistically significant correlation between methodologies ($r = 0.846$, $P < 0.0001$). Infliximab treatment resulted in a statistically significant ($P < 0.001$) decrease in the mean HRAS38 score from 130.5 to 56.5 within 2 weeks of treatment and at 52 weeks of therapy scores were still reduced at 52.5. The mean DAS28(CRP) was also significantly ($P < 0.001$) reduced from a baseline value of 5.8 to 3.7 after 2 weeks treatment with a final value of 3.2 after 52 weeks of therapy. Infliximab reduced the progression of joint destruction by 85%, for terms before infliximab as determined by radiographic analyses. The degree of progression appeared to be associated with the mean HRAS38, although this observation was not shown to be statistically significant by regression analysis ($r = 0.307$). The HRAS38 score comprises minimal and independently acquired parameters and is an effective and comprehensive measure of disease activity in RA patients.

Key words Disease activity · Disease Activity Score with 28 joints (DAS28) · Handy rheumatoid activity score with 38 joints (HRAS38) · Infliximab · Modified Sharp score

H. Kameda (✉) · N. Sekiguchi · H. Nagasawa · K. Amano · H. Takei · K. Suzuki · E. Nishi · H. Ogawa · T. Takeuchi
Division of Rheumatology/Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, 1981 Tsujido-machi, Kamoda, Kawagoe, Saitama 350-8550, Japan
Tel./Fax +81-49-228-3574
e-mail: kamehide@saitama-med.ac.jp

Introduction

The hypothesis that time-integrated disease activity corresponds to organ damage such as joint destruction has been a "central dogma" of inflammatory diseases.[1,2] Thus, a rapid and complete suppression of disease activity, namely, time-differentiated total organ damage, should result in minimal organ damage, and a sustained significant disease activity inevitably leads to progressive organ destruction.

The recent introduction of tumor necrosis factor alpha (TNFα) inhibitory agents to the therapeutic strategy for rheumatoid arthritis (RA) has dramatically improved the outcome for RA sufferers.[3] Smolen et al. recently provided intriguing evidence of the benefit of combination treatment with methotrexate (MTX) plus infliximab, a chimeric anti-TNFα monoclonal antibody, in clinically refractory RA patients using radiographic methods to evaluate disease progression.[4]

To evaluate the relationship between clinical disease activity (or response) and joint destruction in RA patients treated with infliximab, we have to address several issues: (1) the validity of current measures of RA disease activity such as the Disease Activity Score (DAS); the Disease Activity Score of 28 joints (DAS28) and The American College of Rheumatology (ACR) core set, (2) the validity of popular methods of radiographic scoring, and (3) the specificity of the dissociation between disease activity and joint destruction for anti-TNF therapy. The ACR core set is a comprehensive assessment of disease status and is composed of 8 methods of evaluation including radiographic

Table 1. Baseline characteristics of the patients

Disease duration	4–624 months (mean ± SD 111.5 ± 104.7)
Radiographic stage	I: 1, II: 18, III: 8, IV: 32
Functional class	I: 1, II: 26, III: 28, IV: 4
RF	Positive in 50 patients (19–1060 IU/ml)
Number of prior DMARDs	mean ± SD 2.8 ± 1.6 (including MTX)
Duration of MTX	3–235 months (mean ± SD 40.5 ± 44.5)
Weekly MTX dosage	6 mg in 10 patients, 8 mg in 30, 10–20 mg in 19
Folic acid supplementation	25 patients
PSL therapy	50 patients (1–12.5 mg/day, mean ± SD 6.0 ± 2.4 mg/day)

RF, rheumatoid factor; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; PSL, prednisolone

examination.[5] The ACR core set analysis is recommended to be included in clinical trials,[6] but it is rarely applied to RA patients on a daily basis. The DAS score comprises four items including the Ritchie Articular Index (RAI), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), and general health (GH) assessment scored on a visual analog scale (VAS).[7,8] The DAS28 score is a modified form of DAS, and its use in both clinical trials and daily practice may be facilitated by reducing the number of joints to be examined and substitution of RAI with nongraded tender joint count (TJC).[9] Unfortunately, the DAS28 score omits foot and ankle joint assessments, which are affected in more than 50% of RA patients,[10] and may further augment the discrepancy between disease activity scores and van der Heijde-modified Sharp (vdH-Sharp) radiographic scores, because the latter includes foot joints.[11] The inclusion of tender joint count has several disadvantages: (1) it is time-consuming, (2) there is overlap with the patient's global assessment of disease activity, and (3) it is not associated with joint destruction. The recent development of a simplified disease activity index (SDAI), which is the numerical sum of TJC28, SJC28, patient and physician global assessment of disease activity (VAS 0–10 cm), and serum level of C-reactive protein (CRP; mg/dl), did not overcome the defects described above.[12]

Therefore, we developed a new comprehensive measure of RA activity, the handy rheumatoid activity score with 38 joints (HRAS38), which is made up of three mutually independent assessments: (1) patient global assessment of disease activity (PGA), (2) swollen joint score (SJS) of 38 joints, and (3) serum CRP level. We then examined the inhibitory effect of infliximab (3 mg/kg every 8 weeks) added to low-dose (less than 10 mg/week in the majority of patients) MTX on radiographic progression, and it was compared to the 15–25 mg/week of MTX used in Western countries. Finally, the relationship between disease activity (evaluated with HRAS38 and DAS28) and radiographic progression assessed by vdH-Sharp score was investigated.

Patients and methods

Patients

During September 2003 to December 2004, 59 patients with RA who had not been sufficiently controlled with MTX therapy were enrolled in this prospective study. All the patients fulfilled the 1987 classification criteria for RA proposed by the ACR (formerly, American Rheumatology Association).[13] Demographic features of the patients are summarized in Table 1. The mean disease duration was approximately 10 years, and 32 of 59 patients (54%) were radiographically classified as Stage IV according to the criteria of Steinbrocker et al.[14] Most of the patients were functionally classified as Class II or Class III according to the ACR revised criteria for the classification of global functional status in RA.[15] Rheumatoid factor (RF) was positive in the sera of 50 patients (85%). Methotrexate was used as the first (24%), second (25%), or third (24%) disease-modifying antirheumatic drug (DMARD) in the majority of patients. Patients were registered for infliximab therapy if they had not shown a sufficient response to MTX at a dose of 6 mg/week to 20 mg/week) over a minimum of 3 months. A total of 19 patients were receiving MTX at a dose of 10–20 mg/week, a dose that is above the approved dosage by the Japanese Ministry of Health, Labour and Welfare, and 25 patients were taking supplementary folic acid (5–10 mg/week). Notably, 50 patients had been treated with prednisolone (PSL) along with MTX, indicating the active and refractory nature of their disease.

Methods

Patients with active (≥6 of 66 swollen joints, ≥6 of 68 tender joints and either a CRP level of ≥2.0 mg/dl or an ESR of ≥28 mm/1 h) RA despite MTX treatment for a minimum of 3 months were eligible for this prospective study according to the Japanese guidelines for infliximab treatment.[16] Additionally, subjects had to have low risk for opportunistic infections including the following: WBC ≥4000/μl, peripheral blood lymphocyte count ≥1000/μl, and a negative test for serum β-D-glucan. Contraindications for infliximab treatment include: active infection, congestive heart failure, demyelinating disease, and malignancies.[16]

All patients were scheduled to receive infliximab at a dose of 3 mg/kg at weeks 0, 2, 6, and subsequently every 8 weeks. When patients did not show sufficient response to infliximab therapy, the dosage was increased up to 200 mg/kg for patients with less than 60 kg of body weight, and/or the interval of infusion was shortened to 6 weeks. All infusions were given over 2 h with 250 ml of normal saline.

The patients were fully examined at every visit for infusion. The evaluation includes ACR core sets, DAS28(CRP),[17] and HRAS38. The HRAS38 score consists of a cumulative addition of three mutually independent items; PGA (0–100 mm VAS), SJS of 38 joints, and serum CRP level (mg/l). The 38 joints included in the evaluation were 26 joints of DAS28 except for bilateral shoulder joints, as well as 10 metatarsophalangeal (MTP) joints and the bilateral ankle joints. Each joint was scored as follows: 0 = none; 1 = mild (not convincing by observation and confirmed by palpation); 2 = moderate (convincing by observation, but not tense); 3 = severe (tense). Therefore, the SJS score of 38 joints can add up to between 0–114.

We investigated the proportion of patients who met the ACR 20% improvement criteria (achieved an ACR20 response)[18] at week 54, as well as ACR50 and ACR70 responses, DAS28(CRP) and European League Against Rheumatism (EULAR) responses.[19] The hand and foot X-rays were obtained at 0, 30, and 54 weeks. Articular damage and progression were scored according to the method of vdH-Sharp using two expert readers. Radiographic progression was judged using two methods: progression >0.5 and progression > the smallest detectable difference (SDD).[20,21] The SDD for the mean changes from baseline using two readers for each patient's radiographs was 4.39 (the standard deviation of the per-patient differences between the readers divided by the square root of 2) which corresponds to 1% of the maximum vdH-Sharp score, i.e., 448.[22]

Hand X-ray films before infliximab therapy (4–53 months with a mean of 17.4 months) were available for 34 patients, and foot X-ray films were also available for 16 of those patients. Therefore, radiographic progression was calculated as percent of yearly progression of vdH-Sharp; percent in 280 as for the cases of only hand X-ray films, and percent in 448 as for the cases of both hand and foot X-ray films were adjusted according to the interval between the time points of X-ray.[20] The values obtained were then compared with those after infliximab treatment.

Statistical analysis

Statistical analyses were performed using StatView software version 4.5. The Mann–Whitney *U*-test was used for nonparametric comparisons between subgroups, and the paired *t*-test was used for chronological changes in the same items. The difference was considered to be significant when at $P < 0.05$.

Results

Excellent clinical efficacy of infliximab treatment in patients with active and MTX-resistant RA

Of 59 patients included in this study, 3 moved to other hospitals and follow-up was not possible. Two patients withdrew owing to lack of response to therapy. Five patients discontinued infliximab treatment because of adverse events as follows: (1) infusion reaction in 3 patients at 6, 38, and 46 weeks; (2) pneumonia in 1 patient at 6 weeks; and (3) mammary carcinoma in 1 patient at 54 weeks. Three patients were withdrawn for noncompliance to the protocol. In the analysis of ACR 20, 50, and 70 response rates and EULAR response rates, 3 patients who had moved to other hospitals were excluded, and all other patients who discontinued infliximab were regarded as nonresponders.

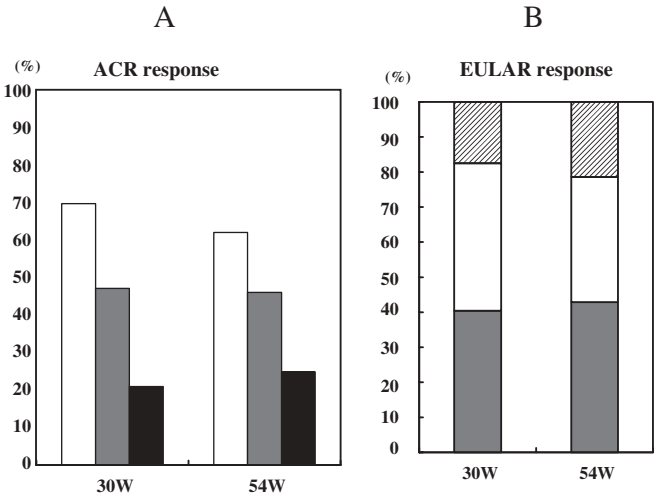

Fig. 1A,B. Overall clinical efficacy of infliximab in 56 patients who were enrolled in this study. **A** The rates of patients who experienced responses according to criteria of American College of Rheumatology (*ACR*) 20% (*open bar*), 50% (*half-solid bar*) and 70% (*solid bar*) improvement criteria at 30 and 54 weeks were evaluated by the nonresponder imputation method, where patients who withdrew were classified as nonresponders. **B** The rates of patients who experienced responses according to the European League Against Rheumatism (*EULAR*) response criteria at 30 and 54 weeks (*W*) were evaluated by the nonresponder imputation method. *Open bar*, moderate responder; *half-solid bar*, good responder; *hatched bar*, nonresponder

Even when stringent assessment criteria and nonresponder imputation analysis were used, the clinical efficacy of infliximab was excellent. The rate of patients who met the 20%, 50%, and 70% improvement criteria of ACR was 70.2%, 47.4%, and 21.1%, respectively, at 30 weeks (Fig. 1A). The rate of patients who experienced good, moderate, and no responses according to the EULAR response criteria at 30 weeks were 40.4%, 42.%, and 17.5%, respectively (Fig. 1B). The clinical efficacy observed at 30 weeks was sustained through to 54 weeks. ACR 20, 50, and 70 response rates were 62.5%, 46.4%, and 25.0%, respectively (Fig. 1A), and the rates of good, moderate, and no responses according to EULAR criteria were 42.9%, 35.7%, and 21.4%, respectively (Fig. 1B).

Development and validation of HRAS38

In this study, we aimed at developing a new comprehensive measure of RA disease activity that could be used for all patients with RA as part of a daily practice, including those receiving biologics. The measure was designed to be predictive of joint destruction. The HRAS38 score constitutes a simple numerical assessment of three mutually independent

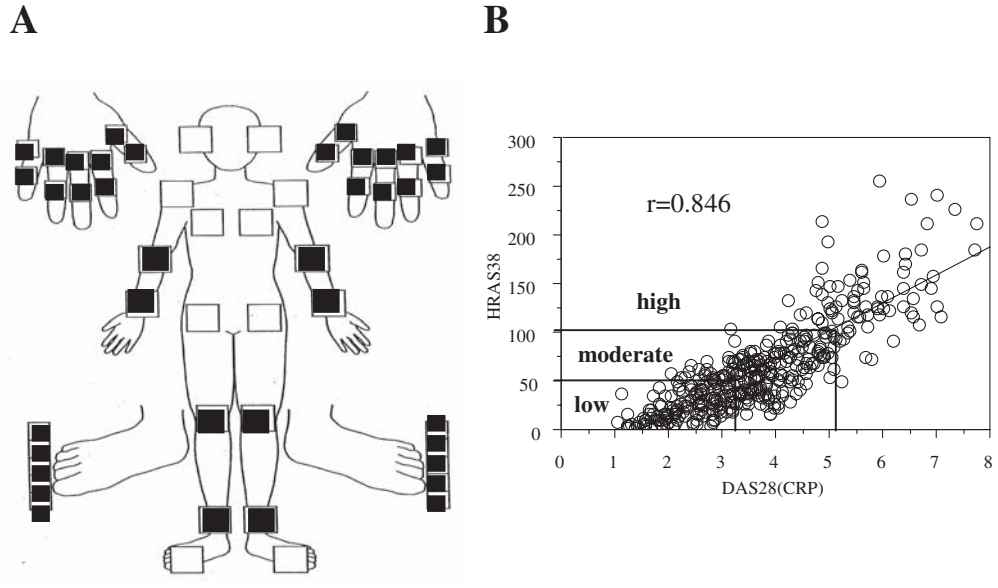

Fig. 2A,B. The values of the handy rheumatoid activity score with 38 joints (*HRAS38*) correlate well with those of disease activity score with 28 joints (*DAS28(CRP)*). **A** Joints examined bilaterally in HRAS38 as indicated by *solid boxes*: elbows, wrists, metacarpophalangeal, proximal interphalangeal, interphalangeal joint of the thumb, ankles, and metatarsophalangeal joints. **B** A total of 414 scatter plots of HRAS38 versus DAS28(CRP) were obtained from nine data points (at weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54) of 46 patients who had been treated with infliximab for 1 year. A linear regression analysis indicated a highly significant degree of correlation between HRAS38 and DAS28(CRP) (r = 0.846). Thus, DAS28(CRP) values of 3.2 and 5.1 almost corresponded to 50 and 100, respectively, in HRAS38

parameters including: (1) PGA (a subjective assessment), (2) SJS of 38 joints (an objective assessment), and (3) serum CRP (a laboratory measurement). Joints that were included in the examination are shown in Fig. 2A.

Comparison of HRAS38 with DAS28(CRP) using linear regression and a total of 414 data from 46 patients (having completed 1-year-infliximab treatment, 9 time points for each patient) revealed a statistically significant linear relationship ($r = 0.846$, $P < 0.0001$; Fig. 2B). The HRAS38 score of the patients with serum CRP level >50 mg/l tended to be higher than that estimated from the value of DAS28(CRP). The linear regression analysis predicts that an HRAS38 value of >100 indicates high disease activity, an HRAS38 value of 50–100 indicates moderate disease activity, and an HRAS38 value of <50 indicates low activity, which are quite consistent with the categorical levels of RA activity defined for DAS28. A change in HRAS38 of greater than or equal to −38 represented major improvement and corresponded to a change of −1.2, which is equivalent to 2 times the measurement error, in DAS28.[22]

Rapid decrease in the value of SJS after infliximab as well as a consequent drop in HRAS38 level

The mean values of TJC and SJC at 0 week were 11.6 and 13.0, respectively, and significantly decreased to 4.4 and 6.3 at 2 weeks after infliximab therapy ($P < 0.001$), 3.0 and 3.7 at 30 weeks, and 1.9 and 2.8 at 54 weeks, respectively (Fig. 3A). As expected, a graded SJS was more sensitive to change than SJC: the mean value of SJS dropped from 31.4 at week 0 to 11.5 at 2 weeks, 8.2 at 30 weeks, and 5.1 at 54 weeks ($P < 0.001$).

HRAS38 showed a very close, but more sharply enhanced, temporal relationship to DAS28(CRP) (Fig. 3B). The mean values of HRAS38 and DAS28(CRP) at week 0 were 131 and 5.8, respectively, and significantly decreased to 56.5 and 3.7 at 2 weeks after infliximab therapy ($P < 0.001$), 54.3 and 3.3 at 30 weeks, and 52.5 and 3.2 at 54 weeks, respectively. Thus, HRAS38 correlated very well to DAS28(CRP) not only at a given time point, but also in temporal changes after an effective therapy.

An 85% inhibition of radiographic progression of disease was observed when infliximab was added to the treatment regimen of patients who were minimally responsive to MTX alone

Before beginning infliximab treatment, percent yearly progression in vdH-Sharp score ranged between 0.1 and 17.9 (mean ± SD; 5.3 ± 4.4) as shown in Fig. 4. The range of percent yearly progression in vdH-Sharp score remarkably decreased to –0.8–4.4 (mean ± SD; 0.8 ± 1.1). Therefore an 85% reduction in the rate of joint destruction as measured by vdH-Sharp score was observed. In addition, 11 patients (32.4%) showed a complete inhibition of disease progression, including an overall radiographic repair (9 patients). Similarly, the mean ± SD of the percent yearly progression in vdH-Sharp score after infliximab in 12 patients, in whom the percent yearly progression in vdH-Sharp just before infliximab was not available, was 0.8 ± 1.0. The percent yearly progression in vdH-Sharp score before infliximab did not correlate to that after infliximab ($r = 0.012$; $P = 0.95$).

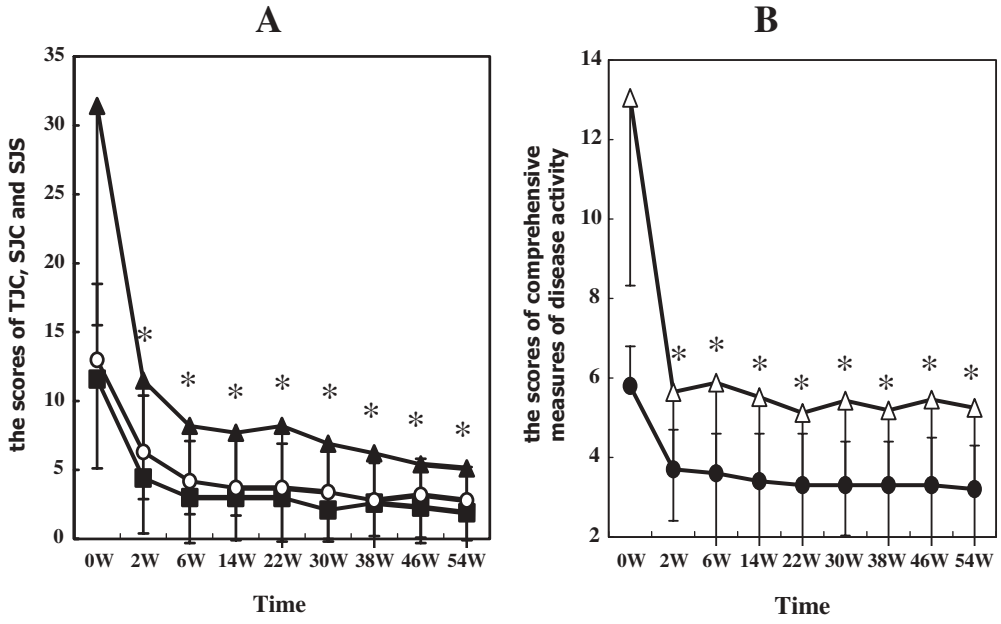

Fig. 3A,B. Rapid clinical response to infliximab in 46 patients who completed a 1-year treatment with infliximab. **A** Tender joint count of 28 joints (*solid squares*), swollen joint count of 28 joints (*open circles*), and swollen joint score of 38 joints (*solid triangles*) significantly decreased at week 2 of infliximab therapy and showed further improvement up to 1 year (*$P < 0.001$ vs the value at week 0). **B** Handy rheumatoid activity score (HRAS38) indicated as $^1/_{10}$ (*open triangles*) and disease activity score (DAS28(CRP)) (*solid circles*) significantly decreased at week 2 of infliximab therapy and the improvement was sustained throughout the year (*$P < 0.001$ vs the value at week 0)

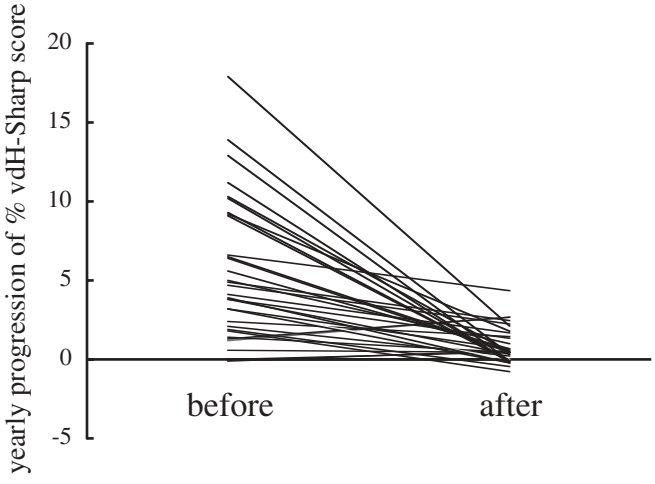

Fig. 4. Dramatic inhibition of the yearly radiographic progression with the addition of infliximab to methotrexate in patients with rheumatoid arthritis. Radiographic progression was calculated as percent yearly vdH-Sharp, and the values before and after infliximab treatment were compared

Little association of radiographic progression during infliximab therapy with a time-integrated disease activity or clinical response to infliximab

Finally, we investigated whether the radiographic progression during infliximab treatment was predictable by continuously measuring disease activity using HRAS38 or DAS28(CRP). Thirty-four patients who had completed a 1-year infliximab treatment were classified into three groups according to the percent yearly progression of vdH-Sharp score after infliximab (Table 2). No progression (<0.5 in yearly progression in vdH-Sharp score) was observed in 12 patients, minimal (statistically nonsignificant) progression (0.5 ≤ yearly progression in vdH-Sharp score ≤ SDD) in 19 patients, and considerable (statistically significant) progression (>SDD) in 15 patients. The titer of RF at week 0, time-integrated serum CRP levels, time-integrated DAS28(CRP) scores, and time-integrated HRAS38 scores tended to be lower, although not statistically significant, in patients with no progression as compared with those patients having minimal progression or considerable progression. The clinical response to infliximab as assessed by ACR50/70 response and EULAR good response at 54 weeks did not correlate to radiographic progression (Table 2).

Discussion

In this study we demonstrated that HRAS38, a newly developed assessment of RA, is adequately sensitive for the evaluation of the disease activity at a single point and for assessing the change in disease activity in response to therapeutic intervention. Moreover, we also confirmed that infliximab therapy effectively inhibits radiographic progression in Japanese patients with active and severe RA.

The development of HRAS38 was driven by the need for a simple, not time-consuming, but comprehensive measurement of RA activity as required in both daily practice and clinical trial assessments. Simplicity in the test method can be introduced by selecting only parameters that are mutu-

Table 2. Correlation of surrogate markers of the mean disease activity and clinical response to radiographic progression during 1-year treatment with infliximab

	No progression $n = 12$, –0.2% ± 0.2%	Minimal progression $n = 19$, 0.5% ± 0.1%	Considerable progression $n = 15$, 2.1% ± 0.8%	
RF (IU/ml)	135.5 ± 138.2	285.2 ± 318.7	244.6 ± 287.5	NS
CRP (mg/dl, mean 0–54 W)	1.3 ± 1.6	1.8 ± 1.5	1.8 ± 1.7	NS
DAS28(CRP), mean 0–54 W	3.4 ± 0.9	3.8 ± 0.6	3.7 ± 1.0	NS
HRAS38, mean 0–54 W	57.0 ± 34.1	64.7 ± 23.7	65.1 ± 29.3	NS
ACR50 response rate (%), 54 W	58.3	47.4	53.3	NS
ACR70 response rate (%), 54 W	33.3	26.3	33.3	NS
EULAR good response (%), 54 W	66.7	42.1	46.7	NS

W, weeks; CRP, C-reactive protein; DAS28, disease activity score with 28 joints; HRAS38, handy rheumatoid activity score with 38 joints; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; NS, not significant

ally independent. In this context, we first selected patient global assessment of disease activity (patient global health) as a subjective measurement because it tends to represent joint pain that is redundantly assessed by tender joint count and patient's global assessment of pain, and it implies disability that is assessed by a Health Assessment Questionnaire (HAQ).

We then selected an objective measurement of joint swelling. Tender joint count, which is largely subjective, was excluded for the above-stated reason. Binary SJC is the prevailing measure of joint swelling, because a previous analysis in which swelling was graded on a scale of 0–3 (0 = normal or none, 1 = minimal or probable, 2 = definite but within joint margin, and 3 = tense or bulging) did not show an advantage over binary evaluation of joint swelling at a given time-point.[23,24] However, a graded examination appears to be more sensitive to change during therapy as compared with a binary one. In fact, an all-or-none assessment of joint swelling disregards a significant decrease in the extent of joint swelling, which is very important in the early assessment of response to a given treatment. Although the grading of the extent of joint swelling may augment intraobserver and interobserver variation, our grading system using observation (inspection) and palpation may minimize this concern. Moreover, the assessment of SJS is not time-consuming as compared with TJC, which mostly depends on patients. We bilaterally excluded sternoclavicular, acromioclavicular, and shoulder joints in consideration of the frequency of involvement, the accuracy of the evaluation of swelling, and the symmetrical weighting of upper and lower extremities.

As a laboratory measure, we included CRP instead of ESR for two reasons: (1) CRP is one of the most reliable measures of the acute phase response and is responsive to changes in tissue damage, and (2) it is less confounded by other factors such as anemia or hypergammaglobulinemia as compared with ESR, therefore more precisely reflecting disease activity.[25] The serum CRP level is rarely above 100 mg/l (10 mg/dl). Indeed, only 2 of 59 patients in this study showed the serum CRP level > 100 mg/l at entry. Because the range of PGA is 0–100 and the range of SJS is 0–114, the contribution of three components of HRAS38 to the total score may be similar.

Clinical efficacy of infliximab for patients with RA is excellent. In the ATTRACT study, 26%–31% of patients with comparable disease duration (7–9 years) to our study achieved ACR50 response at 30 weeks, while only 5% of patients who received placebo (MTX alone) met ACR50 improvement criteria.[26] Despite a significantly lower dose of MTX and the limitation of infliximab dose (up to 3 mg/kg every 8 weeks) as compared with the ATTRACT study, our patients showed a slightly more favorable response to infliximab (Fig. 1A). The efficacy of infliximab plus MTX was also demonstrated in the ASPIRE study, in which patients with active and poor-prognostic RA of ≤3 years' duration were enrolled.[27]

Radiographic results showed the most dramatic results with the mean increase in vdH-Sharp score of 7.0 at 54 weeks in the MTX-placebo group in the ATTRACT study and 3.7 in the ASPIRE study. The mean increase in vdH-Sharp score in patients treated with MTX plus 3 mg/kg infliximab every 8 weeks was only 1.3 in the ATTRACT study[28] and was 0.4 in the ASPIRE study.[27] A similar level of reduction in the radiographic progression was observed with infliximab therapy in both studies (81% in the ATTRACT study[28] and 89% in the ASPIRE study[27]), and was confirmed by our study which demonstrated an 85% reduction in structural damage (Fig. 4) despite the fact that our patients demonstrated the most rapid progression of joint destruction before infliximab with the average yearly progression rate of 23.7 in vdH-Sharp score, much higher than that demonstrated in the ATTRACT study (6.4–8.0) or the ASPIRE study (10.1–10.5).

The clinical response to infliximab (Figs. 1 and 3) was better than that of MTX or bucillamine, as we have previously reported,[29,30] in terms of both responder rate and rapidness of response. It may be reasonable, therefore, to suggest that the prevention of structural damage by infliximab is superior to that observed by conventional DMARDs including MTX as demonstrated previously[27,28] and also confirmed in this study (Fig. 4).

However, recent subanalysis of the ATTRACT study provides intriguing evidence of the radiographic benefit of combination treatment with infliximab plus MTX in RA patients who had no clinical improvement to MTX alone.[4] Mean change in vdH-Sharp score was 6.0 in ACR20 responders and 7.2 in ACR20 nonresponders in the MTX plus placebo-treated group, while it was 0.1 in ACR20 responders and 1.2 in ACR20 nonresponders in the infliximab plus MTX-treated group. We classified our patients according to

their 1-year-changes in vdH-Sharp score and compared the titer of rheumatoid factor, mean values of CRP, DAS28(CRP) and HRAS38, as well as clinical response at 54 weeks among the groups. The rates of ACR50 or ACR 70 responder at 54 weeks, as well as the rate of EULAR good response at 54 weeks, were similar among three groups (Table 2). The analysis using less stringent response criteria such as ACR20 response and EULAR moderate response also showed comparable results (data not shown).

Although not statistically significant, patients who exhibited minimal or considerable radiographic progression tended to have a higher RF titer and higher mean values of CRP, DAS28(CRP), and HRAS38. Therefore, our results indicate that the infliximab plus MTX therapy significantly (ca. 85%) inhibits joint damage through disease activity-control-dependent and -independent pathways. In this context, recent observations of isolated inhibition of bone erosion despite unaffected synovitis in studies of experimental arthritis models manipulating osteoclasts were very interesting.[31–33] Thus, the association of time-integrated HRAS38 with radiographic progression may be more evident in RA patients receiving conventional DMARD such as MTX, which should be examined in the future investigations.

In conclusion, HRAS38 is a simple and convenient measure of RA activity and can be substituted for DAS28 in daily practice and clinical trials. Infliximab therapy effectively controls RA activity and joint destruction in Japanese patients receiving a relatively lower dose of MTX as compared with that in Western countries. A time-integrated HRAS38 may be associated with radiographic progression, as well as a time-integrated DAS28(CRP), although infliximab therapy is likely to minimize the association of disease activity with structural damage.

Acknowledgment This study was supported by a grant from the Japanese Ministry of Health, Labour and Welfare.

References

1. van den Berg WB, van Riel PLCM. Uncoupling of inflammation and destruction in rheumatoid arthritis: myth or reality? Arthritis Rheum 2005;52:995–9.
2. van Leeuwen MA, van der Heijde DMFM, van Rijswijk MH, Houtman PM, van Riel PLCM, van de Putte LBA, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. J Reumatol 1994;21:425–9.
3. Takeuchi T, Amano K, Kameda H. Impact of TNF inhibitors on rheumatoid arthritis. Inflammation Regeneration 2006;26:148–59.
4. Smolen JS, Han C, Bala M, Maini RN, Kalden JR, van der Heijde D, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement. Arthritis Rheum 2005;52:1020–30.
5. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993;36:729–40.
6. Boers M, Tugwell P, Felson DT, van Riel PLCM, Kirwan JR, Edmonds JP, et al. A World Health Organization and Interstitial league of Association for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. J Rheumatol 1994;21(suppl 41):86–9.
7. van der Heijde DMFM, van't Hof MA, van Riel PLCM, Theunisse LAM, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916–20.
8. van der Heijde DMFM, van't Hof MA, van Riel PLCM, van Leeuwen MA, van Rijswijk MH, van de Putte LBA. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis 1992;51:177–81.
9. Prevoo MLL, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LBA, van Riel PLCM. 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.
10. American College of Rheumatology Committee on outcome measures in rheumatoid arthritis clinical trials. Reduced joint count in rheumatoid arthritis clinical trials. Arthritis Rheum 1994;37:463–4.
11. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999;26:743–5.
12. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, van Riel PL, Tugwell P. A simplified activity index for rheumatoid arthritis for use in clinical practice. Rheumatology 2003;42:244–57.
13. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
14. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140:659–62.
15. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum 1992;35:498–502.
16. Miyasaka N, Takeuchi T, Eguchi K. Proposed Japanese guidelines for the use of infliximab for rheumatoid arthritis. Mod Rheumatol 2005;15:4–8.
17. DAS-score NL. Home of the DAS. http://www.das-score.nl/www.das-score.nl/.
18. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.
19. van Gestel AM, Prevoo MLL, van't Hof MA, van Rijswijk MH, van de Putte LBA, van Riel PLCM. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Arthritis Rheum 1996;39:34–40.
20. van der Heijde D, Simon L, Smolen J, Strand V, Sharp J, Boers M, et al. How to report radiographic data in randomized clinical trials in rheumatoid arthritis: Guidelines from a roundtable discussion. Arthritis Rheum 2002;47:215–8.
21. Lassere M, Boers M, van der Heijde D, Boonen A, Edmonds J, Saudan A, et al. Smallest detectable difference in radiological progression. J Rheumatol 1999;26:731–9.
22. van Gestel AM, Haagsma CJ, van Riel PLCM. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845–50.
23. Fuchs HA, Brooks RH, Callahan LF, Pincus T. A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. Arthritis Rheum 1989;32:531–7.
24. Fuchs HA, Pincus T. Reduced joint counts in controlled clinical trials in rheumatoid arthritis. Arthritis Rheum 1994;37:470–5.
25. Otternass IG. The value of C-reactive protein measurement in rheumatoid arthritis. Semin Arthritis Rheum 1994;24:91–104.
26. Maini E, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase III trial. Lancet 1999;354:1932–9.
27. St. Clair EW, van der Heijde DMFM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis. A randomized, controlled trial. Arthritis Rheum 2004;50:3432–43.

28. Lipsky PE, van der Heijde DMFM, St. Claire EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594–602.
29. Kameda H, Amano K, Sekiguchi N, Takei H, Ogawa H, Nagasawa H, et al. Factors predicting the response to low-dose methotrexate therapy in patients with rheumatoid arthritis: a better response in male patients. Mod Rheumatol 2004;14:442–6.
30. Sekiguch N, Kameda H, Amano K, Takeuchi T. Efficacy and safety of bucillamine, a D-penicillamine analogue, in patients with active rheumatoid arthritis. Mod Rheumatol 2006;16:85–91.
31. Schett G, Redlich K, Hayer S, Zwerina J, Bolon B, Dunstan C, et al. Osteoprotegerin protects against generalized bone loss in tumor necrosis factor-transgenic mice. Arthritis Rheum 2003;48:2042–51.
32. Lubberts E, van den Bersselaar L, Oppers-Walgreen B, Schwarzenberger P, Coenen-de Roo CJ, Kolls JK, et al. IL-17 promotes bone erosion in murine collagen-induced arthritis through loss of the receptor activator of NF-κ B ligand/osteoprotegerin balance. J Immunol 2003;170:2655–62.
33. Pettit AR, Ji H, von Stechow D, Muller R, Goldring SR, Choi Y, et al. TRANCE/RANKLE knockout mice are protected from bone erosion in a serum transfer model of arthritis. Am J Pathol 2001; 159:1689–99.