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Predictive Factors Related to the Efficacy of Golimumab in Patients with Rheumatoid Arthritis

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ABSTRACT: In order to investigate the predictive factors related to clinical efficacy and radiographic progression at 24 weeks by looking at the serum levels of tumor necrosis factor (TNF)-α and interleukin (IL)-6 including baseline characteristics in patients with rheumatoid arthritis (RA) treated with golimumab, serum concentrations of TNF-α and IL-6 were analyzed every 4 weeks up to 24 weeks in 47 patients treated with golimumab. Baseline levels of the Disease Activity Score 28 C-reactive protein (DAS28-CRP) and Simplified Disease Activity Index (SDAI) scores were also assessed. Radiographic progression using the van der Heijde-modified Sharp (vdH-S) score was assessed in 29 patients. Multiple regression analyses related to the DAS28-CRP score and delta total sharp score at 24 weeks was undertaken using the baseline characteristics of patients and serum concentrations of matrix metalloproteinase (MMP)-3, TNF-α, and IL–6. The DAS28-CRP score and SDAI decreased significantly at 4 weeks up to 24 weeks compared with baseline. Serum levels of TNF-α were not changed significantly up to 24 weeks compared with baseline, but those of IL-6 decreased significantly at 4 weeks up to 8 weeks. Multiple regression analyses showed that disease duration and serum levels of MMP-3 were related significantly to the DAS28-CRP score at 24 weeks. Radiographic progression was related significantly to disease duration with regard to joint space narrowing and bone erosion. However, serum levels of TNF-α and IL-6 were not correlated significantly with the DAS28-CRP score and radiographic progression. These data suggest that decreasing serum levels of IL-6 significantly, MMP-3, and disease duration are predictive factors for RA activity in patients taking golimumab.

KEYWORDS: golimumab, IL-6, rheumatoid arthritis, TNF-α

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Introduction

Treatment of rheumatoid arthritis (RA) has been developed so that remission is possible for a long time and structural damage to joints is reduced using tumor necrosis factor (TNF) blockade.[1] The effect of the human monoclonal antibody golimumab in RA has been evaluated mainly in large Phase III clinical trials involving patients with previous exposures to different therapies.[1–3] The GO-BEFORE (Golimumab Before Employing Methotrexate as the First-line Option in the Treatment of Rheumatoid Arthritis of Early Onset) study involved patients with active RA who were naïve to methotrexate (MTX). The GO-FORWARD (Golimumab in Active Rheumatoid Arthritis Despite Methotrexate Therapy) study involved patients with active RA despite MTX therapy. The GO-AFTER (Golimumab in Patients with Active Rheumatoid Arthritis After Treatment with Tumor Necrosis Factor α Inhibitors) study involved patients with active RA who had previously received anti-TNF α therapy.[1–3] Such studies of clinical efficacy were useful when considering therapy with golimumab. However, how serum concentrations of cytokines such as TNF-α and interleukin (IL)-6 are influenced by treatment with golimumab, and the factors related to its

efficacy (including radiographic progression) against RA are not known.

Based on the hypothesis that anti-TNF-α therapy with golimumab induces changes in serum levels of TNF-α and IL-6, we measured these concentrations every 4 weeks for up to 24 weeks. We then evaluated the relationship between the levels of these cytokines and clinical factors to predict the efficacy of golimumab against RA.

Patients and Methods

Analyses of clinical efficacy related to serum levels of TNF-α and IL-6. Forty-seven patients (51–75 years of age) were diagnosed as having RA according to the criteria set by the American College of Rheumatology (ACR)[4]: active disease for ≥3 months despite previous use of disease-modifying antirheumatic drugs (DMARDs) (naïve; 11 patients), or treatment with biologic agents (number of patients who switched, 36). Switched cases from other biologic treatments (infliximab, 5; etanercept, 7; adalimumab, 5; tocilizumab, 6; abatacept, 13) were also included. The Disease Activity Score 28 C-reactive protein (DAS28-CRP) and Simplified Disease Activity Index (SDAI) scores were also noted.[5,6] All patients gave their written, informed consent to participate in the research, which was approved by the Tokyo Women's Medical University ethics committee (No. 1321). The research was conducted in accordance with the principles of the Declaration of Helsinki.

Patients were screened for latent and active tuberculosis. Those infected by the hepatitis-B or hepatitis-C virus were excluded. Forty-seven patients (40 women) treated with golimumab (50 mg for 36 patients; 100 mg for 11 patients) every month had been treated for >24 weeks (range 24–92 weeks) and had a mean age of 64.7 years (range 37–79 years), with a mean duration of disease of 16.9 years (range 5–18 years).

The baseline levels of DAS28-CRP, SDAI scores,[6] and HealthAssessmentQuestionnaire-DisabilityIndex(HAQ-DI) were 4.34 ± 0.69, 23.6 ± 5.58, and 1.13 ± 0.79, respectively (Table 1). The mean titer of the anticyclic citrullinated peptide (CCP) antibody was 146 ± 95.2 (positive rate 87.1%). The mean rheumatoid factors were present in 76% of the positives by rheumatoid arthritis particle agglutination (RAPA) (584.8 ± 903.6).

Thirty-six patients received 50 mg and 11 subjects received 100 mg of golimumab every month plus mean values of 6.69 mg/week of MTX (0–16 mg) and 4.74 mg/day of prednisolone (PSL) (0–10 mg). One-hundred milligrams of golimumab was administered mainly to the patients who could not take MTX. Fifty milligrams of golimumab was used for the patients who could take MTX concomitantly. According to the criteria set by Steinbrocker et al.[7], 16 patients, 30 patients, and 1 patient taking golimumab were classified as having class II, III, and IV disease, respectively. CRP and MMP-3 were measured in our hospital in the usual manner. High sensitivity to TNF-α (normal range, 0–2.8 pg/mL) in serum was measured by enzyme-linked immunosorbent assay (ELISA) using a Quantikine HS Human TNF-α Immunoassay kit, and IL-6 (normal range, 0–4 pg/mL) was measured by the CLEIA method using IL-6 cartridges at SRL Co. ROC (receiver operating characteristic) analysis was performed to acquire the cut-off points with sensitivity and specificity related to the significant clinical factors.

Table 1. Baseline patient demographics and disease characteristics.

CHARACTERISTICS	mean (SD)
Patients, n	47
Female, n (%)	40 (85.1)
Age, years	64.7 (9.93)
Disease duration, years	16.9 (11.3)
Swollen joint count (0–66)	5.76 (2.07)
Tender joint count (0–66)	5.33 (1.79)
Patient's global assessment (VAS; 0–100 mm)	51.6 (20.7)
Physician's global assessment (VAS; 0–100 mm)	59.9 (12.6)
CRP, mg/dl	1.09 (1.5)
DAS28 (CRP)	4.34 (0.69)
CDAI	22.3 (5.48)
SDAI	23.6 (5.58)
HAQ-DI	1.13 (0.79)
TNF-α, pg/ml	16.6 (45.6)
IL-6, pg/ml	23.3 (57.7)
Anti-CCP antibody, (%)	146 (87.1)
MTX, mg/w (%)	6.69 (68.1)
PSL, mg/d (%)	4.74 (1.98)

Radiographic assessment. Radiographs of the hands and feet were obtained at baseline and at 24 weeks. Radiographs were scored using the van der Heijde-modified Sharp (vdH-S) score.[8] For these analyses, progression was defined as patients having changes from baseline in the total vdH-S score >0.5 units at week 24. This definition of radiographic progression is a commonly used threshold in studies of patients with inflammatory arthritis.[9,10]

Radiographs of hands and feet were obtained for 29 subjects (23 women and 6 men; mean age, 64.7 ± 10.3 years). The mean duration of disease was 13.9 ± 11.2 years. The mean DAS28-CRP score at baseline and 24 weeks was 4.15 ± 0.51 and 2.79 ± 1.19, respectively. The mean SDAI at baseline and at 24 weeks was 21.9 ± 4.44 and 9.72 ± 6.47, respectively. The mean serum level of TNF-α at baseline and at 24 weeks was 7.76 ± 29.5 and 16.2 ± 14.1 pg/mL, respectively. The mean serum level of IL-6 at baseline and at 24 weeks was 10.4 ± 8.69 and 10.9 ± 16.8 pg/mL, respectively. The mean serum level of matrix metalloproteinase-3 (MMP-3) at baseline and at 24 weeks was 108 ± 100 and 121 ± 121 ng/mL, respectively. The mean HAQ-DI score at baseline and at 24 weeks was 0.96 ± 0.702 and 0.996 ± 0.749, respectively. The mean MTX and PSL usages were 6.32 ± 3.22 mg/week and 4.50 ± 1.53 mg/day, respectively. One patient had stage I

disease; 10 had stage II; 7 had stage III; and 11 had stage IV. The ΔTSS was measured at baseline and at 24 weeks to calculate rapid radiographic progression (RRP) and rapid radiographic improvement (RRI). The definition of RRP was a ΔTSS >2.5, and that of RRI was a ΔTSS <0 at 24 weeks. Apparent significant improvement in radiographic features in those treated with golimumab and MTX was also investigated.

Statistical analyses. The Willcoxon method was used to examine nonparametric continuous variables between the baseline values of the DAS28-CRP score as well as the serum levels of TNF-α and IL-6 every 4 weeks up to 24 weeks. Multiple regression analyses related to the DAS28-CRP score and ΔTSS were carried out at 24 weeks compared with baseline as well as Spearman correlation methods using StatFlex version 6.0. A *P*-value of <0.05 was considered significant. The ROC curve was calculated to acquire the sensitivity and specificity with odds ratio of the clinical factors by the above software.

Results

Clinical outcome and changes in serum concentrations of TNF-α and IL-6. The DAS28-CRP score decreased significantly at 4 weeks ($P < 0.001$) up to 24 weeks (Fig. 1A). The SDAI also decreased significantly at 4 weeks ($P < 0.001$) up to 24 weeks (Fig. 1B). Remission with regard to the DAS28-CRP score and SDAI was seen in 26.7% and 22.2% of subjects at 24 weeks, respectively. There is no significant difference between women and men regarding DAS28(CRP) at baseline ($P = 0.316$) and 24 weeks ($P = 0.975$), 85.1% of them being women, as shown in Table 1.

The mean ± SD serum level of TNF-α (pg/mL) was 16.6 ± 45 at baseline, 11.2 ± 9.7 at 4 weeks, 11.7 ± 5.6 at 8 weeks, 15.1 ± 14 at 12 weeks, 17.7 ± 21 at 16 weeks, 18.9 ± 18 at 20 weeks, and 19.4 ± 25 at 24 weeks (Fig. 2). The serum level of TNF-α was not significantly different between the baseline level and at 4 weeks ($P = 0.368$), 8 weeks ($P = 0.457$), 12 weeks ($P = 0.828$), 16 weeks ($P = 0.839$), 20 weeks ($P = 0.708$), or 24 weeks ($P = 0.670$) (Fig. 2). Comparison of serum levels of TNF-α showed significant differences between naïve and switched cases at baseline (naïve 23.4 ± 52.1; switched 15.4 ± 43.9 pg/mL; $P = 0.04432$) and no significant difference at 24 weeks (naïve 18.9 ± 16.3; switched 16.1 ± 11.5 pg/mL; $P = 0.81805$). Therefore, naïve cases at baseline showed significantly high serum levels of TNF-α.

The mean ± SD serum level of IL-6 (pg/mL) was 23.3 ± 57 at baseline, 9.0 ± 10 at 4 weeks, 12.5 ± 18 at 8 weeks, 11.4 ± 13 at 12 weeks, 15.5 ± 21 at 16 weeks, 21.5 ± 60 at 20 weeks, and 21.7 ± 60 at 24 weeks (Fig. 3). Serum levels of IL-6 decreased significantly at 4 weeks ($P = 0.007$) and at 8 weeks ($P = 0.046$). However, a significant difference was not recognized at 12 weeks ($P = 0.204$), 16 weeks ($P = 0.769$), 20 weeks ($P = 0.57$), or 24 weeks ($P = 0.412$) compared with baseline. Comparison of serum levels of IL-6 showed no significant difference between naïve and switched cases at baseline (naïve 21.6 ± 43.2; switched 30.4 ± 67.5 pg/mL; $P = 0.394$) and at 24 weeks (naïve 14.9 ± 22.3; switched 11.3 ± 16.3 pg/mL; $P = 0.923$). Multiple regression analyses related to the DAS28-CRP score at 24 weeks revealed *P*-values for age 0.123; disease duration 0.041; serum level of TNF-α 0.492; serum level of IL-6 0.211; serum level of MMP-3 0.0103; and for naïve patients 0.764 (Table 2). Therefore, disease duration and the DAS28-CRP score at 24 weeks was correlated significantly ($P = 0.041$, $r = 0.239$) (Fig. 4A). The serum level of MMP-3 at baseline and the DAS28-CRP score at 24 weeks were also correlated significantly ($P = 0.0103$; $r = 0.319$) (Fig. 4B). The serum level of MMP-3 was correlated to the serum level of IL-6 at baseline ($P = 0.0028$; $r = 0.109$). The serum level of IL-6 and the DAS28-CRP score at 24 weeks was also correlated significantly ($P = 0.0203$, $r = 0.196$). The relationship between survival and continuation of golimumab treatment by the Kaplan–Meier method was 0.88 ± 0.050 (Fig. 5A). The prevalence of continuation was not significantly different between those taking MTX ($n = 32$) and those not ($n = 15$) (log-rank test, $P = 0.8188$). Based on the low disease activity (LDA) at cut-off point at 2.0 pg/mL (within normal) of TNF-α (sensitivity 0.7, specificity 0.542, odds ratio 2.76) and

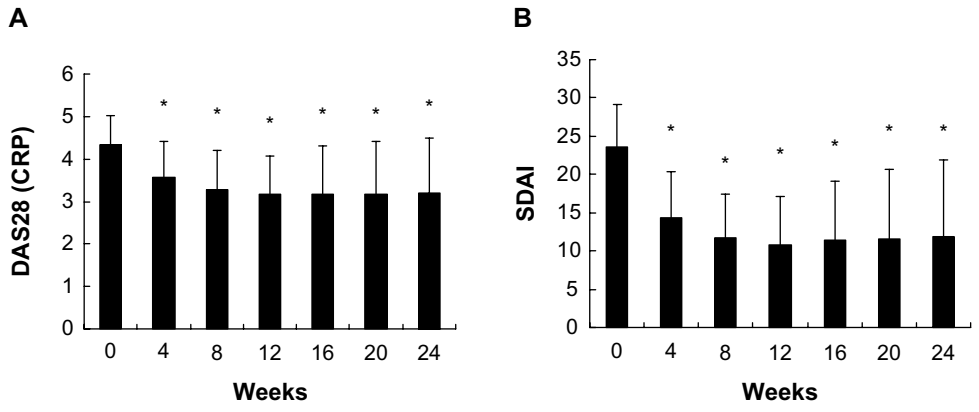

Figure 1. The DAS28-CRP score (**A**) and SDAI (**B**) after golimumab treatment for up to 24 weeks.
Note: *Significant difference compared with baseline ($P < 0.05$).

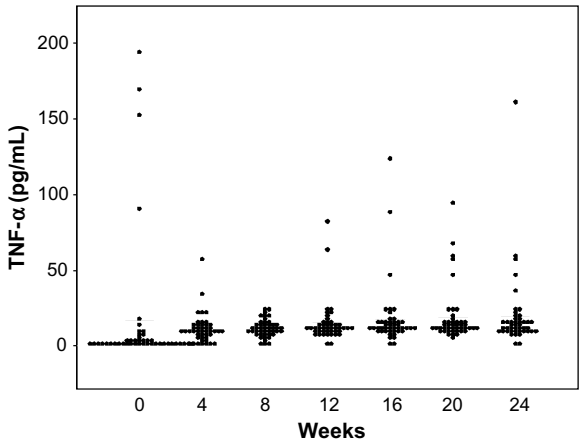

Figure 2. Serum levels of TNF-α after golimumab treatment for up to 24 weeks.
Note: The bar shows mean values of the data.

cut-off point of 12.2 pg/mL of IL-6 (sensitivity 0.7, specificity 0.5, odds ratio 2.33), no relationship was found between DAS28(CRP) at 24 weeks and TNF-α or IL-6 at baseline. In the ROC analysis, disease duration at cut-off point at 5 years showed sensitivity 0.526, specificity 0.546, and odds ratio 1.33; and MMP-3 at cut-off point at 138 mg/mL showed sensitivity 0.714, specificity 0.417, odds ratio 1.79.

Radiographic outcome and related factors at 24 weeks. The mean TSS at baseline and 24 weeks was 160.4 ± 111 and 159.7 ± 112.2, respectively (P = 0.2985). The mean ΔTSS, joint space narrowing, and erosion scores were −0.69 ± 3.51, −0.66 ± 2.47, and 0.03 ± 1.57, respectively. RRP was seen in 17.2% (5/29) of subjects, and RRI was observed in 44.8% (13/29) of subjects according to cumulative probability plots (Fig. 6A). Inhibition of RRP (ΔTSS ≤0.5) was seen in 68.97% (20/29) of subjects. Multiple regression analyses showed a relationship between the ΔTSS and age (P = 0.9802), disease duration (P = 0.0233) as well as serum levels of CRP (P = 0.5721), TNF-α (P = 0.1426), IL-6 (P = 0.8314), MMP-3 (P = 0.2143), and MTX usage (P = 0.3696), respectively. Therefore, disease duration was significantly correlated with the ΔTSS at 24 weeks (Fig. 6B and C) (P = 0.0027 by Spearman). Disease duration was correlated significantly with joint space narrowing (P = 0.023, r = 0.375) and bone-erosion score (P = 0.016, r = 0.477). Comparison of the ΔTSS showed a significant difference between the 50-mg (−0.125 ± 3.3, n = 36) and 100-mg groups (−3.4 ± 3.5, n = 11) (P = 0.04131). Changes in joint space narrowing showed a significant difference between 50-mg (−0.25 ± 2.3) and 100-mg (−2.6 ± 2.3) (P = 0.02719) groups; however, changes in bone erosion were not significantly different between the two groups (50 mg, 0.083 ± 1.7; 100 mg, −0.2 ± 0.45) (P = 0.64373).

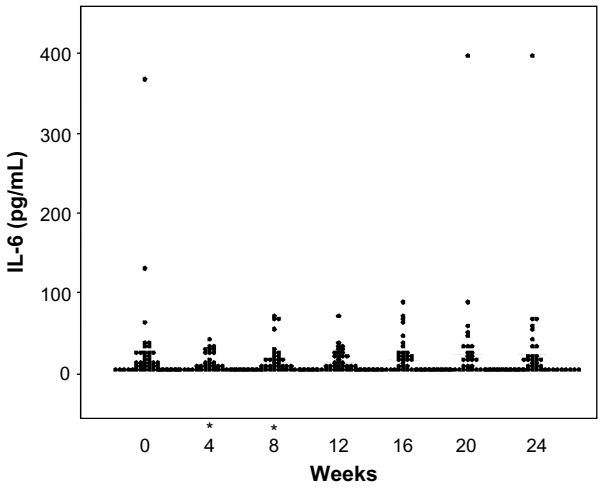

Figure 3. Serum level of IL-6 after golimumab treatment for up to 24 weeks.
Notes: *Significant difference with baseline (P < 0.05). The bar shows mean values of the data.

Table 2. Multiple regression analysis to DAS28 (CRP).

FACTORS AT BASELINE	DAS28 (CRP) AT BASELINE		DAS28 (CRP) AT 24 WEEKS	
	P-VALUE	RC	*P*-VALUE	RC
Disease duration	0.533	0.005	0.0408	0.041
TNF-α	0.510	−0.003	0.4915	0.006
IL-6	0.172	0.002	0.2107	0.003
MMP-3	0.001	0.003	0.0103	0.06
Naïve	0.975	−0.008	0.7639	−0.80

Abbreviations: DAS28 (CRP), disease activity score 28 (C-reactive protein); TNF, tumor necrosis factor; IL, interleukin; MMP, matrix metalloprotease; RC, regression coefficient.

Apparent significant improvement in radiographic features in a patient treated with golimumab and MTX. In one patient, bone erosion was clearly improved. He was 58 years of age with stage II and class 2 disease. He had RA for 2 years and had the following data at baseline: DAS28-CRP score, 4.5; SDAI, 23.8; serum level of CRP, 0.79 mg/dL; erythrocyte sedimentation rate (ESR), 42 mm/hour; serum level of MMP-3, 109 ng/mL; serum level of TNF-α, 3.5 pg/mL; serum level of IL-6, 13.0 pg/mL; RAPA titer, 320; anti-CCP antibody, 245 mg/L; and TSS, 96.

He then took 50 mg of golimumab and 12 mg/week of MTX for 52 weeks (Fig. 7). He was naïve, and his values at 24 weeks were DAS28-CRP score, 1.2; SDAI, 1.0; serum level of CRP, 0.00 mg/dL; ESR, 11 mm/hour; serum level of MMP-3, 102 ng/mL; serum level of TNF-α, 8.7 pg/mL; serum level of IL-6, 2.2 pg/mL; and TSS, 88 at 24 weeks. The ΔTSS and changes in joint space narrowing and bone erosion score were −8, −3, and −5, respectively. Bone erosion of the proximal interphalangeal (PIP) joint in his right hand showed dramatic remodeling and repaired in a time-dependent manner (Fig. 7B and C). The radiographic shadow of soft-tissue swelling of the PIP joint was clearly improved with bone repair (Fig. 7).

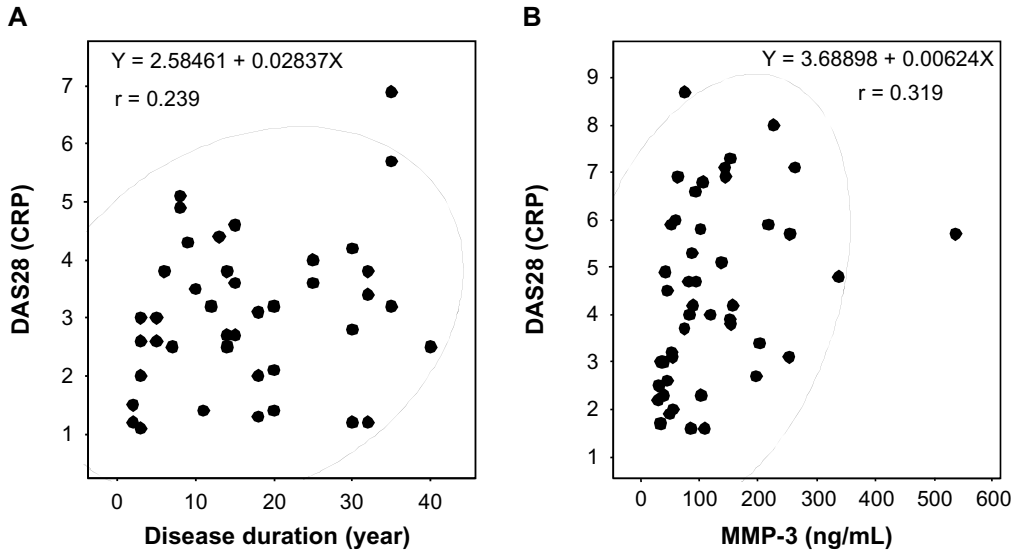

Figure 4. (**A**) Relationship between the DAS28-CRP score and disease duration. (**B**) Relationship between the DAS28-CRP score and serum level of MMP-3.

Discussion

Takeuchi et al reported that the serum concentration of golimumab at 24 weeks and response rates were lowest in patients with serum concentrations of golimumab <0.24 μg/mL but increased with increasing serum concentration of golimumab through to 24 weeks in Japanese patients in the GO-MONO study.[11] Also, serum levels of golimumab increased in a dose-proportional manner; steady state was reached at week 12 in that study.[11]

In the present study, serum levels of IL-6 decreased significantly 4 and 8 weeks after golimumab administration. Therefore, the serum level of IL-6 may be inhibited before the steady state of the golimumab level has been reached. In sub-analyses of the serum levels of TNF-α, we found that taking MTX and having a short duration of disease were related to a significant decrease in serum levels of TNF-α in a time-dependent manner (data not shown). These findings supported the notion that golimumab was more effective with an adequate dose of MTX to block TNF-α in early RA.[1]

It was reported that a multibiomarker disease activity (MBDA) test performed well in the assessment of disease activity in RA patients in the Computer Assisted Management for Early Rheumatoid Arthritis (CAMERA) study in patients treated with intensive or conventional MTX-based treatment strategies.[12] Serum levels of IL-6 and MMP-3 were found to be correlated with the DAS28-CRP score, swollen joints count (SJC) 28, and tender joints count (TJC) 28, respectively, but the serum level of MMP-3 was not correlated with visual analog scale-general health (VAS-GH).

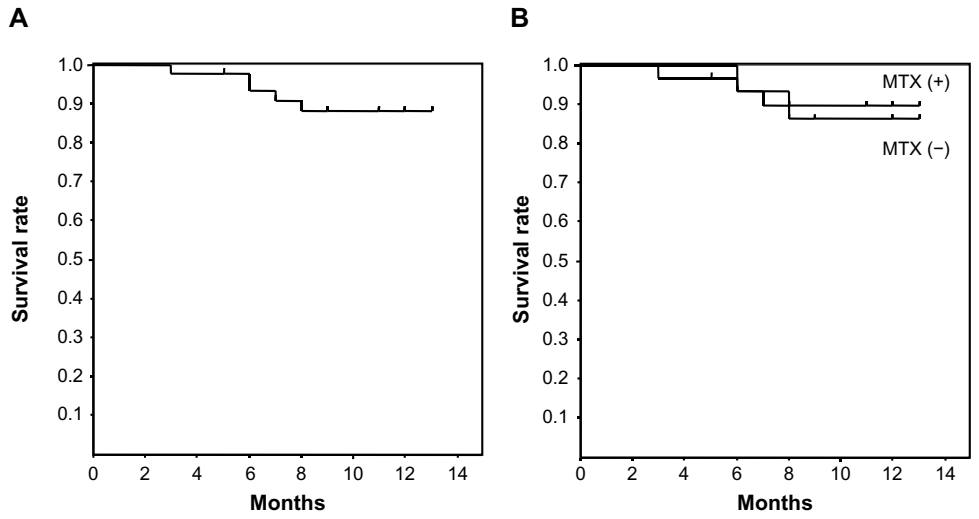

Figure 5. Prevalence of continuation up to 52 weeks of treatment by the Kaplan–Meier method. Total number ($n = 47$) (**A**) and comparison between the MTX ($n = 32$) and non-MTX ($n = 15$) group (**B**).

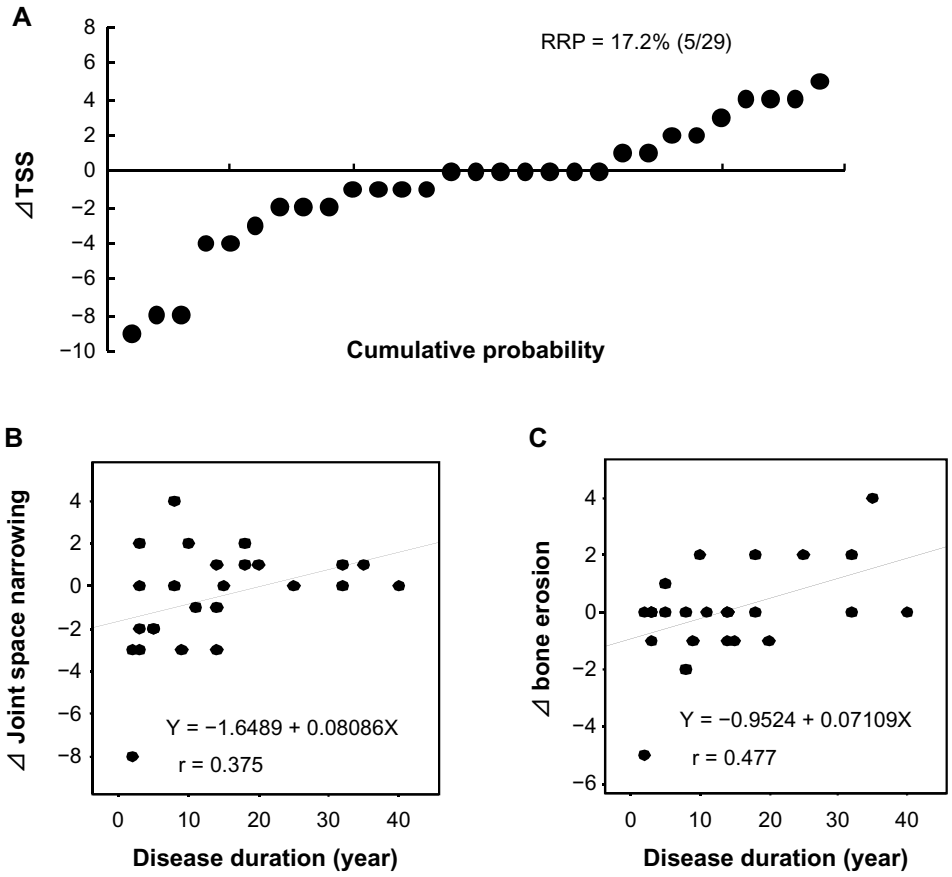

Figure 6. Cumulative probability plots upon treatment with golimumab ($n = 29$). (**A**) RRP (rapid radiographic progression). Relationship between disease duration and changes in joint space narrowing (**B**) or changes in bone erosion (**C**).

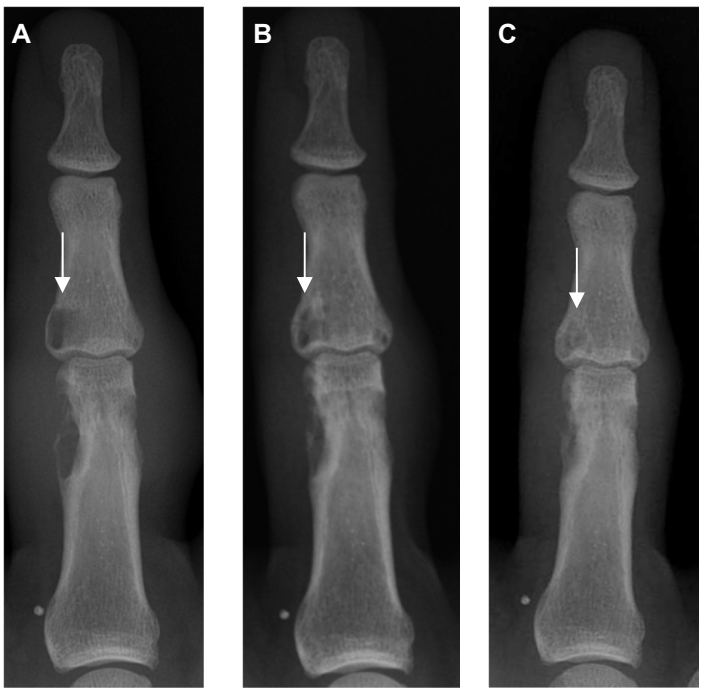

Figure 7. Apparent improvement in radiologic features at baseline (**A**), 24 weeks (**B**), and 52 weeks (**C**) after treatment with golimumab and MTX. Arrow shows significant improvement of bone erosion at the proximal interphalangeal (PIP) joint of the right hand.

This MBDA test was also not predictive of radiographic progression.

We found that disease duration was significantly related to the ΔTSS for joint space narrowing and bone erosion upon treatment with golimumab at 24 weeks. Sub-analyses of the GO-BEFORE study were carried out to ascertain whether specific biomarkers were associated with radiographic progression in MTX-naïve patients with RA administered with MTX monotherapy or golimumab.[13] The researchers could not find biomarkers correlated with golimumab therapy, but levels of epidermal growth factor and CD40L correlated significantly in the MTX monotherapy group.[13] About 70% of patients in the GO-BEFORE study had a disease duration ≤3 years,[13] but our patients had a mean duration of disease of 16.5 years. Such differences in patient backgrounds might have influenced the predictive factors of golimumab treatment.

It is also reported that golimumab plus MTX was significantly more effective than MTX monotherapy in Japanese patients with active RA despite MTX therapy in the GO-FORTH study.[14] Remission according to DAS28-ESR was seen in 30/86 (34.9%) of subjects at 24 weeks with MTX (6–8 mg/week).[14] Remission according to the DAS28-CRP score was 26.7% in the present study. In the GO-MONO study, the DAS28-CRP score was 17.2% for those taking 50 mg golimumab and 19% for those taking 100 mg golimumab.[7] Recently, in the GO-MORE study involving 3,366 patients, remission was seen in 25% of patients after 6 months of golimumab treatment.[15] Based on the data in our study, MTX usage (68.1%) could influence the prevalence of remission (26.7%). However, in the present study, the patients who could not take MTX gave reasons such as allergic reactions, rash, diarrhea, severe oral ulcers, or liver dysfunction.

Multiple regression analyses revealed that the serum level of MMP-3 at baseline was related significantly to the DAS28-CRP score at 24 weeks. Therefore, the serum level of MMP-3 could be a predictive factor for the efficacy of golimumab in clinical practice. The serum level of MMP-3 was correlated to the serum level of IL-6 at baseline. The serum level of IL-6 and the DAS28-CRP score at 24 weeks were also correlated significantly. These data suggest that the serum levels of MMP-3 and IL-6 at baseline may be predictive factors related to the DAS28-CRP score at 24 weeks. To overcome high serum levels of MMP-3 at baseline, an adequate dose MTX could help to suppress serum concentrations of MMP-3 and IL-6. Another predictive factor of clinical efficacy was disease duration, indicating that golimumab could be used in the early stage of RA. Thus, the serum level of IL-6 decreased significantly upon golimumab treatment in RA, but neither the serum levels of TNF-α nor of IL-6 could be used to predict disease activity. Additional long-term analyses are needed to explore further the effect of golimumab in RA patients.

The major limitations of the present study are that the study cohort was small and the study design was retrospective. This is the first report of the relationship between serum levels of TNF-α or IL-6 up to 24 weeks of treatment with golimumab and radiographic progression. Further investigations are needed to ascertain the efficacy and kinetics of cytokines in patients taking 50 mg and 100 mg of golimumab.

In summary, decreasing serum levels of IL-6 significantly compared with baseline, MMP-3, and disease duration were predictive factors for RA activity in patients taking golimumab. In particular, disease duration was related to radiographic progression upon golimumab treatment in RA patients.

Author Contributions

Conceived and designed the experiments: KK. Analyzed the data: KK. Wrote the first draft of the manuscript: KK. Contributed to the writing of the manuscript: KK. Agree with manuscript results and conclusions: KK, JC, YI, MT, AY. Jointly developed the structure and arguments for the paper: KK, JC, YI, MT, AY. Made critical revisions and approved final version: KK. All authors reviewed and approved of the final manuscript.

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