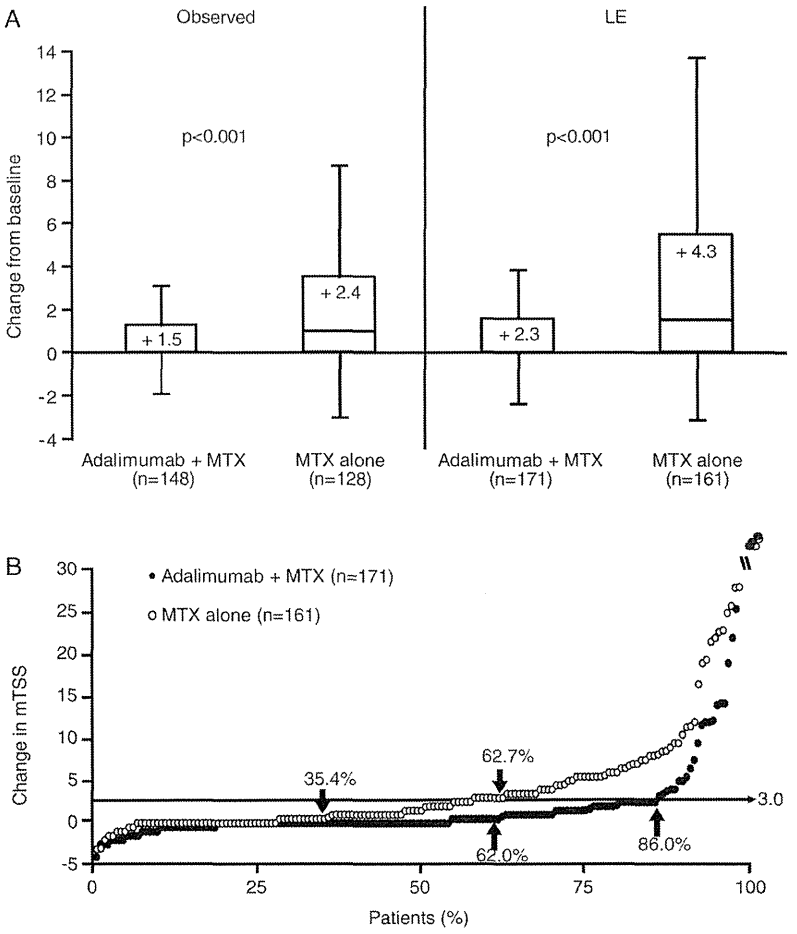

Figure 2 (A) Box plot of change from baseline in mTSS at week 26 with adalimumab+MTX versus MTX alone and (B) cumulative probability plot of mean change from baseline to week 26 in mTSS score (LE). Thickened horizontal lines in (A) indicate median values, the boxes mark the interval between the 25th and 75th percentiles, whiskers indicate the IQR and mean values are reported in the boxes. No radiographic progression (change from baseline in mTSS≤0.5) was reported in 62.0% (106/171) of adalimumab+MTX patients versus 35.4% (57/161) of MTX alone patients (p<0.001). No clinically relevant radiographic progression (change from baseline mTSS≤3) was reported in 86.0% (147/171) of adalimumab+MTX patients versus 62.7% (101/161) of MTX alone patients (p<0.001) (B). LE, linear extrapolation; mTSS, modified total Sharp score; MTX, methotrexate. p Value determined using Wilcoxon rank sum test.

Safety

The mean treatment duration during the double-blind phase was 168.7±36.6 days for adalimumab+MTX patients (mean cumulative adalimumab dose, 477.4±104.5 mg) and 162.8±38.6 days for MTX alone patients. Overall, there were 376 and 302 AEs reported in the adalimumab+MTX group and the MTX alone group, respectively. There were no significant differences in the percentage of patients with AEs in the adalimumab+MTX group (80.7% (138/171)) versus the MTX alone group (71.8% (117/163)), and the incidence of severe AEs was rare (table 2). No significant differences in the incidence of AEs of interest were observed between the two groups, with the exception of injection-site reactions, which were reported in 10.5% of adalimumab+MTX patients and 3.7% of MTX alone patients (p=0.02; table 2). Serious infections were observed in two adalimumab+MTX patients (one case each of pneumonia and infectious enteritis) and one MTX alone patient (*Pneumocystis jiroveci* pneumonia), occurring at rates of 2.5 and 1.4 events per 100 patient-years, respectively. There were no reports of demyelination, tuberculosis or malignancy during the study. One death, due to worsening of interstitial lung disease, occurred in the MTX alone group.

DISCUSSION

The HOPEFUL 1 study was designed to evaluate the efficacy and safety of adalimumab in combination with MTX in Japanese patients with early RA. This is the first description of a clinical trial of anti-TNF therapy+MTX versus MTX alone in MTX-naive Japanese patients with early RA and high disease activity. It is also the first randomised trial evaluating the efficacy of anti-TNF therapy+low-dose MTX versus low-dose MTX alone for the inhibition of radiographic progression in any patient population. This study extends observations from Western studies of adalimumab by demonstrating the superiority of adalimumab+MTX to MTX alone for the inhibition of radiographic progression and improvement in clinical outcomes in Japanese patients with early RA. Moreover, the combination of adalimumab+MTX significantly improved a wide array of clinical and functional disease activity measures and responses versus MTX alone, with improvements observed as early as the first assessment (week 2) and maintained through the 26-week double-blind trial.

Following 26 weeks of treatment, the mean ΔmTSS (primary endpoint) in adalimumab+MTX patients (1.48) in the current study was significantly smaller than observed in MTX alone patients (2.38). In addition, a similar trend in inhibition of radiographic progression in patients with early RA was observed in the OPTIMA study, with a smaller mean ΔmTSS in adalimumab+MTX patients (0.15) versus MTX alone patients (0.96; p<0.001).[12] The difference between the two treatment groups (0.8) at week 26 was similar to the difference observed in the current study (0.9 (observed)).[12] Furthermore, baseline characteristics, including RA duration, in the two studies were generally similar, but the OPTIMA study had a lower percentage of previous DMARD use.

A similar trend in inhibition of radiographic progression in the current study was observed in the PREMIER study, with a

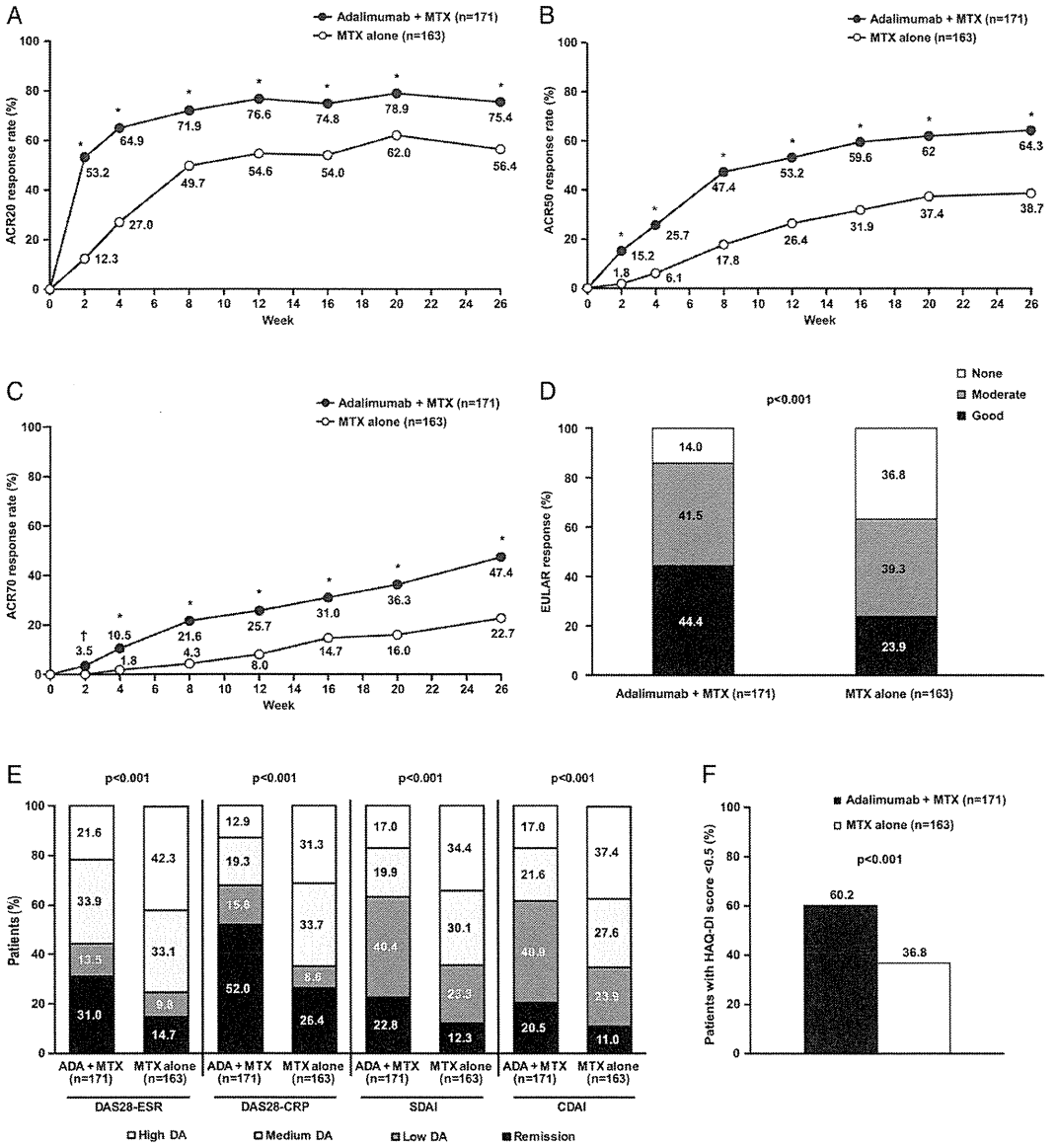

Figure 3 Percentage of patients with an (A) ACR20 response, (B) ACR50 response or (C) ACR70 response over time; (D) the percentage of patients with a EULAR response at week 26; (E) the percentage of patients with low, medium or high disease activity at week 26; and (F) the percentage of patients achieving functional remission (HAQ-DI score<0.5) at week 26. The following values were used to identify remission, low, medium and high disease activity for each clinical assessment in (E): DAS28-ESR or DAS-CRP (<2.6, ≥2.6–<3.2; ≥3.2–≤5.1, >5.1, respectively), SDAI (≤3.3, >3.3–≤11.0, >11.0–≤26.0, >26.0, respectively), and CDAI (≤2.8, >2.8–≤10.0, >10.0–≤22.0, >22.0, respectively). *p<0.001 versus MTX alone. †p=0.03 versus MTX alone. ACR, American College of Rheumatology; ADA, adalimumab; CDAI, clinical disease activity index; DA, disease activity; DAS28-CRP, disease activity score using a 28-joint count and C reactive protein level; DAS28-ESR, disease activity score using a 28-joint count and erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ-DI, Health Assessment Questionnaire disability index; MTX, methotrexate; SDAI, simplified disease activity index.

smaller mean ΔmTSS in adalimumab+MTX patients (0.8) versus MTX alone patients (3.5; p<0.001). However, the mean difference in radiographic progression between the two treatments groups, although statistically significant, was smaller in the current study (0.9 (observed); 2.0 (LE)) than in the PREMIER study (2.7).

In the current study, the SD for the mean ΔmTSS at week 26 was generally high. When the median ΔmTSS was compared using observed data, results were in good agreement between the PREMIER study (0.0 (adalimumab+MTX) vs 1.3 (MTX alone); data on file) and the current study (0.0 (adalimumab +MTX) vs 1.0 (MTX alone)). Alternatively, the smaller difference in improvement observed in the current study may also be related to the mTSS scoring method used, but this seems unlikely because only two joints assessed in PREMIER were omitted from scoring in the present analysis. The mean duration of RA was also shorter in the current study (0.3 years) versus the PREMIER study (0.7–0.8 years), although the percentage of patients who had previously taken DMARDs was higher (43.3–53.4% vs 31.5–32.5%). There were also slight differences in mean baseline tender and swollen joint counts and CRP levels, which were higher in the PREMIER study and considered

Table 2 Adverse events (AEs)

Parameter	Patients (n (%)) Adalimumab+MTX (n=171)	MTX (n=163)
Any AE	138 (80.7)	117 (71.8)
Severe AE	1 (0.6)	1 (0.6)
Serious AE	7 (4.1)	4 (2.4)
Infectious AE	59 (34.5)	48 (29.4)
Serious infection	2 (1.2)	1 (0.6)
AEs leading to study drug discontinuation	7 (4.1)	6 (3.7)
AEs of interest		
Elevated liver function test level	32 (18.7)†	21 (12.9)†
Injection-site reaction	18 (10.5)*	6 (3.7)
Haematological event	7 (4.1)	8 (4.9)
Allergic reaction	1 (0.6)	2 (1.2)
Interstitial lung disease	1 (0.6)	1 (0.6)
Lupus-like syndrome	0	1 (0.6)
Opportunistic infection	0	1 (0.6)

*p=0.02 versus MTX.
†≥94% of events were mild in severity.
MTX, methotrexate.

related to the longer duration of RA at baseline versus the current study. Furthermore, the MTX dose of 6–8 mg/week, although consistent with the dosage commonly administered in Japan at the time the study was conducted, was substantially lower than that commonly administered in Western countries (eg, 15–20 mg/week). In the PREMIER study, MTX was initiated at 7.5 mg/week, increased to 15 mg/week during weeks 4–8, and increased to 20 mg/week starting at week 9. In addition, the mean MTX dose during the 26 weeks of the current study was significantly lower in the adalimumab+MTX group (6.2±0.8 mg/week) versus the MTX alone group (6.6±0.6 mg/week; $p<0.001$), thereby potentially impacting the ΔmTSS and thus the maximal difference observed between the two treatment groups. Therefore, these multiple differences may have contributed to the small difference in radiographic outcomes between the current study and the PREMIER study. Whether the difference in radiographic outcomes can be explained by differences between Japanese and Western populations remains unclear, although this seems unlikely. Longer-term studies may help elucidate potential differences in outcomes.

Since this study was conducted, the maximum approved MTX dosage in Japan has been increased from 8 to 16 mg/week in patients with RA. Therefore, this study provides important information on the efficacy of low-dose MTX and anti-TNF therapy versus low-dose MTX alone for the inhibition of radiographic progression. Data suggest that patients with early RA who may not tolerate higher doses of MTX will likely benefit from adalimumab+low-dose MTX combination therapy.

Given the lower MTX dose prescribed, one could question whether we might only be seeing natural progression in the MTX only arm. It is ethically difficult to include a true placebo arm in clinical trials of ≥6 months duration for early active RA, particularly when MTX is recommended as first-line therapy to achieve clinical remission/low disease activity. Although an important question to ponder, a placebo arm in long-term clinical trials in early active RA appears to be unrealistic, and further research using highly sensitive and reproducible imaging techniques during a short-term placebo-treatment period in early active RA is warranted.

It is also important to note that the current patient population had severe baseline symptoms, including baseline erosions, despite only several months since RA onset. This scenario is becoming increasingly less common in Western populations due to treat-to-target recommendations and earlier intervention. In Japan, general practitioners are still seeing many early RA patients and referrals to rheumatologists are often delayed. In addition, the diagnosis of RA in this trial was based upon 1987 classification criteria. Thus, these factors may have played a role in the conundrum of more severe baseline clinical symptoms yet shorter mean disease duration.

The clinical results of the current study are supported by the HARMONY study, which retrospectively determined the effectiveness and safety of adalimumab 40 mg every other week with or without MTX (mean dose, 8.5 mg/week) in Japanese patients with RA (mean RA duration, 9.0±9.5 years) with or without prior biologic treatment.[15] Although patients in the HARMONY study had more established disease and the study design was retrospective, adalimumab+MTX patients (n=143) had an improvement from baseline in DAS28-ESR score at week 24 (baseline, 5.3; week 24, 3.3), which was within the range but slightly smaller than the improvement observed in the current study at week 26 (baseline, 6.6; week 26, 3.7; see online supplementary figure 1A). Clinical remission rates for adalimumab+MTX patients were also comparable between the HARMONY study (week 24, 35.0%) and the current study (week 26, 31.0%).

The safety profile of the current study was generally consistent with those in previous clinical studies of adalimumab in patients with RA conducted in Japan.[14–16] There were no reports of demyelination, tuberculosis or malignancy, and there were no statistically significant differences in the incidence of serious AEs, serious infections, opportunistic infections or lupus-like reactions between adalimumab+MTX patients versus MTX alone patients. There was a significantly higher incidence of injection-site reactions for adalimumab+MTX patients versus MTX alone patients, but the incidence (10.5%) was similar to that reported for the 167 adalimumab±MTX patients in the HARMONY study (12.0%). The incidence of injection-site reactions in both of these studies was lower than the 30.8% reported for the 91 adalimumab monotherapy patients (40 mg every other week) in the CHANGE study,[14] possibly related to the immunosuppressive effects of concomitant MTX in the current study and in some of the patients in the HARMONY study.

In the multivariate regression analyses (see online supplementary table 1), lower baseline CRP level was identified as a predictor of radiographic non-progression in adalimumab+MTX patients, whereas normal baseline CRP level (≤0.3 mg/dl) appeared to have an increased likelihood of radiographic non-progression. However, no baseline predictors appeared to predict both the lack of progression and clinical remission. Furthermore, baseline mTSS was not an independent predictor for either treatment group in this study.

Overall, adalimumab+MTX was well tolerated in Japanese patients with early RA with no new safety signals and with a safety and tolerability profile similar to that observed in Western populations. Administration of adalimumab in combination with MTX was efficacious in improving radiographic and clinical responses in MTX-naive patients with early RA, high disease activity and poor prognostic factors (eg, rheumatoid factor positive or with baseline erosive damage) through week 26. Given its radiographic, clinical and functional superiority versus MTX monotherapy, consideration should be given to administration

of anti-TNF-α and MTX combination therapy in patients with early RA and high disease activity.

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Adalimumab, a human anti-TNF monoclonal antibody, outcome study for the prevention of joint damage in Japanese patients with early rheumatoid arthritis: the HOPEFUL 1 study

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Notes

Baseline levels of soluble interleukin-6 receptor predict clinical remission in patients with rheumatoid arthritis treated with tocilizumab: implications for molecular targeted therapy

Interleukin-6 (IL-6) is a monomeric protein that binds to either soluble or membrane-bound IL-6 receptors (IL-6R)[1 2] Tocilizumab, a humanised anti-IL-6R monoclonal antibody, binds to soluble IL-6R (sIL-6R) and membrane-bound IL-6R, blocking signal transduction pathways through competitive

Table 1 Differences in baseline characteristics between sIL-6R-low and sIL-6-high patients

Characteristics	All (n=43)	Baseline sIL-6R		p Value
		sIL-6R-low (n=19)	sIL-6R-high (n=24)	
Age, years	60 (52–67)	57 (45–66)	61 (53–70)	0.33
Gender, female, n (%)	38 (88)	17 (89)	21 (88)	1.00
Disease duration, years	4.5 (2.2–7.9)	5.2 (3.7–7.9)	3 (1.8–8.0)	0.47
Concomitant methotrexate, n (%)	14 (33)	5 (26)	9 (38)	0.52
Methotrexate dose, mg/week	8 (7.1–10)	8 (6–9)	8 (7.75–10)	0.36
Glucocorticoid use, n (%)	14 (33)	5 (26)	9 (38)	0.52
DAS28-ESR	5.1 (4.2–5.9)	4.77 (3.94–6.05)	5.16 (4.46–5.78)	0.51
SDAI	19.78 (14.85–27.99)	19.78 (12.45–27.99)	19.79 (15.32–28.13)	0.59
CDAI	18.3 (13.8–25.2)	18.3 (11.8–26.7)	18.1 (14.2–25.0)	0.73
TJC, 28 joints	5 (3–6)	4 (2–6)	5 (3–7.75)	0.32
SJC, 28 joints	5 (3–8)	5 (3–9)	5 (3–7.5)	0.61
Patient global VAS, mm	45 (23–65)	39 (15–70)	46 (35–64)	0.35
Physician global VAS, mm	41 (26–59)	39 (32–55)	45 (25–60)	0.62
CRP, mg/dL	0.49 (0.13–2.80)	0.45 (0.17–2.21)	0.57 (0.13–3.20)	0.41
ESR, mm/h	46 (19–65)	46 (18–59)	46 (19–69)	0.85
HAQ-DI	1 (0.500–1.250)	1 (0.375–1.500)	1 (0.500–1.125)	0.96
RF value, IU/mL	68 (27–121)	71 (28–106)	65 (17–150)	0.95
Anti-CCP antibody value, IU/mL	141 (17–>300)	94 (19–>300)	238 (16–>300)	0.49
MMP-3 value, ng/mL	104 (60–219)	68 (51.5–260)	113 (60–218)	0.77
IL-6, pg/mL	4.70 (1.51–8.54)	1.82 (1.15–13.2)	5.99 (2.88–8.35)	0.28

Data are shown as median (IQR) or number of patients (%). Statistical differences between median values were analysed by Wilcoxon rank-sum test. Differences in percentage values were analysed by Fisher's exact test.
CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; CRP, C-reactive protein; DAS28, disease activity score with 28 joint counts; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire–disability index; IL, interleukin; MMP-3 matrix metalloproteinase 3; RF, rheumatoid factor; SDAI, simplified disease activity index; sIL-6R, soluble interleukin-6 receptor; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

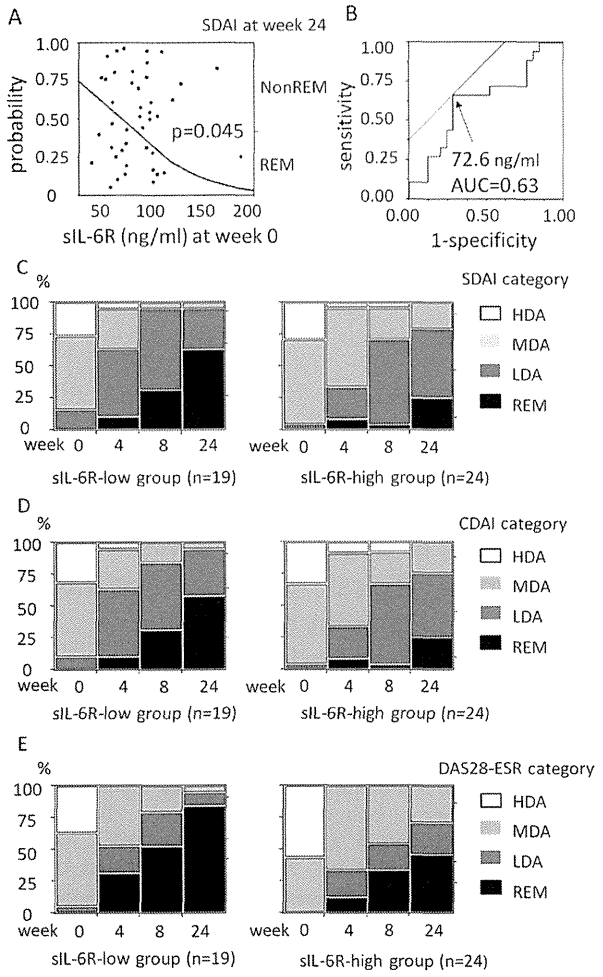

Figure 1 (A) Logistic regression analysis showing the predicted probability of achieving Simplified Disease Activity Index (SDAI) remission at week 24 as a function of sIL-6R at week 0. (B) ROC curve showing a cut-off sIL-6R level of 72.6 ng/mL discriminated between remission and non-remission at week 24, with a sensitivity of 67% and a specificity of 72%. Percentage of patients categorised by SDAI (C), Clinical Disease Activity Index (CDAI) (D), and DAS28-ESR (E) in sIL-6R-low and sIL-6R-high groups at weeks 0, 4, 8, and 24. AUC, area under the curve; CDAI, Clinical Disease Activity Index; DAS28, disease activity score with 28 joint counts; ESR, erythrocyte sedimentation rate; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; REM, remission; ROC, receiver operating characteristic; SDAI, Simplified Disease Activity Index; sIL-6R, soluble interleukin-6 receptor.

inhibition of IL-6 binding.[3] We have previously demonstrated that baseline plasma tumour necrosis factor (TNF) levels are associated with the clinical response to infliximab, anti-TNF monoclonal antibody binding to soluble and membrane-bound TNF.[4] Therefore, it is tempting to speculate that baseline serum levels of sIL-6R, rather than those of IL-6, are associated with clinical response to tocilizumab in patients with rheumatoid arthritis (RA). To test this hypothesis, we analysed serum levels of IL-6 and sIL-6R before tocilizumab treatment in our institution and evaluated their association with clinical remission.

Consecutive patients with RA in our institution who commenced 8 mg/kg tocilizumab treatment every 4 weeks as the first biologic agent between March 2010 and April 2012 were included. At baseline, serum levels of IL-6 and sIL-6R were measured by electrochemiluminescence assay with the Ultra-Sensitive Kit (Meso Scale Discovery, Maryland, USA). In this assay, immunoglobulin inhibiting reagent (Bioreclamation, New York, USA) was used to block heterophilic antibody interference.[5]

The baseline clinical characteristics of the 43 enrolled patients are shown in table 1. Median Simplified Disease Activity Index (SDAI) decreased from 19.78 at baseline to 4.71 at week 24, resulting in SDAI remission in 18 (42%) patients. Median (IQR) IL-6 and sIL-6R at baseline were 4.70 (1.51–8.54) pg/mL and 84.2 (62.2–98.0) ng/mL, respectively. Baseline levels of sIL-6R were not associated with other parameters (data not shown). Univariate logistic regression analysis revealed that the baseline sIL-6R level was an only significant predictor of SDAI remission at week 24 ($p=0.045$; figure 1A). Multivariate analysis confirmed us that sIL-6R was solely a significant predictor (data not shown). A cut-off sIL-6R level of 72.6 ng/mL discriminated between SDAI remission and non-remission with a sensitivity of 67% and a specificity of 72% (figure 1B), Clinical Disease Activity Index (CDAI) remission with 65% and 69%, and disease activity score with 28 joint counts, erythrocyte sedimentation rate (DAS28-ESR) remission with 59% and 81%, respectively. The numbers of patients with baseline sIL-6R values of ≤72.6 ng/mL (sIL-6R-low) and >72.6 ng/mL (sIL-6R-high) were 19 and 24, respectively. We could not find significant differences in baseline characteristics between the two groups (table 1).

SDAI category changes in sIL-6R-low and sIL-6R-high patients are shown in figure 1C. A significantly higher proportion of patients in sIL-6R-low group achieved SDAI remission compared with those in sIL-6R-high (63% and 25%, respectively; $p=0.02$ by Fisher's exact test). CDAI and DAS28-ESR category changes are also shown (figure 1D,E). Although the difference in the remission rate of CDAI was marginal between groups (58% in the sIL-6R-low group and 25% in the sIL-6R-high group, respectively; $p=0.06$), that of DAS28-ESR at week 24 was again significant (84% vs 46%, respectively; $p=0.01$). Response rate, as assessed by American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria, was numerically better in sIL-6R-low group, although not statistically significant (data not shown).

Baseline levels of sIL-6R predicted clinical remission in RA patients treated with tocilizumab without showing associations with disease activity as shown in previous reports.[6 7] Our results suggest that the amount of target molecule could be considered as one of the predictors when using molecular targeted therapy. This finding could be of help for establishing treatment strategies with tocilizumab, achieving higher remission rate as early as possible along with the treat-to-target recommendation.

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Contributors All the authors evaluated the study results, interpreted the data and suggested additional analyses. All authors contributed to the development and critical review of manuscript and approved the final version.

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Patient consent Obtained.

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Baseline levels of soluble interleukin-6 receptor predict clinical remission in patients with rheumatoid arthritis treated with tocilizumab: implications for molecular targeted therapy

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Concise report

Distinct arthropathies of the hands in patients with anti-aminoacyl tRNA synthetase antibodies: usefulness of autoantibody profiles in classifying patients

Yuko Kaneko[1], Hironari Hanaoka[1], Michito Hirakata[2], Tsutomu Takeuchi[1] and Masataka Kuwana[1]

Abstract

Objective. The aim of this study was to characterize arthropathies of the hands associated with anti-aminoacyl tRNA synthetase (ARS) autoantibodies.

Methods. Fifty-six patients with anti-ARS antibodies were selected from consecutive patients who visited Keio University Hospital between1983 and 2011, based on their joint symptoms and the availability of hand X-rays. Their clinical characteristics, anti-CCP antibodies, RF, and hand X-ray findings were retrospectively examined.

Results. Based on characteristic hand X-ray findings, the anti-ARS-positive patients with joint symptoms could largely be categorized into three groups. The predominant group (64%) was patients with no significant X-ray findings. The remaining patients with destructive changes were classified into two distinct groups. One group had mainly erosions in the PIP and MCP joints and/or ankylosis of the wrists with anti-CCP and RF, which is consistent with the features of RA. The other group showed subluxation of the thumbs and periarticular calcification that was independent of anti-CCP or RF, which is exclusively found in anti-Jo-1-positive patients.

Conclusion. Autoantibody profiles, including anti-CCP, RF and individual anti-ARS specificities, are useful in classifying anti-ARS-associated arthropathies of the hands into RA or anti-Jo-1-related disorders.

Key words: arthropathy, anti-aminoacyl tRNA synthetase antibodies, anti-CCP antibody.

CLINICAL SCIENCE

Introduction

Idiopathic inflammatory myopathies are often accompanied by joint symptoms, but these are usually mild and do not destroy joints like RA [1]. Arthritis is observed more frequently in patients with anti-aminoacyl tRNA synthetase (ARS) autoantibodies than in those without [2]. There have been four patterns of articular involvement reported in patients with anti-ARS antibodies, including arthralgia alone, non-erosive arthritis without subluxation, non-erosive arthritis with subluxation and erosive polyarthritis [2, 3].

Arthritis with subluxation was first described by Bunch *et al.* [4] and Oddis *et al.* [5] as a subluxing arthropathy associated with anti-Jo-1 antibodies. It is characteristically a deforming, yet predominantly non-erosive arthropathy associated with subluxation of the IP joints, especially of the thumbs (referred to as floppy thumb) and often accompanied with periarticular calcinosis [3–5]. There have been several case reports of anti-Jo-1-positive patients with remarkably destructive erosive arthropathies [3, 6, 7]. The characteristics of the erosive arthropathy with anti-Jo-1 are quite different from those of RA in terms of the distribution of affected joints. Specifically, the anti-Jo-1-associated arthropathy mainly affects DIP joints and is frequently accompanied by subluxation with

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little erosion. In contrast, some case reports have described anti-Jo-1-positve patients with severe erosions in the PIP, MCP and DIP joints along with the presence of anti-CCP antibodies. However, there is controversy as to whether these erosive arthropathies are associated with an anti-ARS antibody itself or concomitant RA. Moreover, it has now been recognized that serum autoantibodies target multiple ARS, including Jo-1 (histidyl tRNA synthetase), PL-7 (threonyl tRNA synthetase), PL-12 (alanyl tRNA synthetase), EJ (glycyl tRNA synthetase), OJ (isoleucyl tRNA synthetase) and KS (asparaginyl tRNA synthetase), and each anti-ARS has unique characteristics [8]. Previous reports focusing on articular involvement have been limited to the anti-Jo-1 antibody, and it is still unclear whether there are common articular characteristics associated with anti-ARS antibodies. The aim of this current study is to characterize arthropathies of the hands associated with anti-ARS antibodies, focusing on structural damage and autoantibody profiles.

Subjects and methods

We assessed 11 884 patients suspected of having CTD who visited Keio University Hospital and whose serum samples were sent to our ANA laboratory between 1983 and 2011 for eligibility in this study. The patients were enrolled based on (i) being positive for anti-ARS antibodies, including antibodies to Jo-1, EJ, OJ, PL-7, PL-12 and KS by immunoprecipitation assay, and (ii) the presence of joint symptoms. Among 102 patients with anti-ARS antibodies, a total of 60 patients had had joint symptoms, but 4 of them were excluded because of the unavailability of hand X-rays. Consequently we enrolled 56 patients. The demographic and clinical information on all patients were retrospectively obtained by review of their medical charts. This study was approved by the Keio University ethics committee and all patients agreed to participate in the study and provided written informed consent.

Individual anti-ARS antibodies were detected by immunoprecipitation assay with HeLa cell extracts, as previously described [8]. RF was measured using a latex-enhanced immunonephelometric assay kit (Eiken Chemical, Tochigi, Japan) and anti-CCP antibodies were measured using an ELISA kit (Medical & Biological Laboratories, Nagano, Japan). The upper limits of the normal ranges for the kits were 15 IU/l and 4.5 U/ml, respectively.

Hand X-rays were blinded and read by two readers independently (Y.K. and M.K.). If there were any discrepancies between their readings, they discussed the findings until reaching an agreement. The findings of erosion, subluxation, ankylosis and periarticular calcinosis were recorded separately in 15 joints, including the second to fifth DIP, second to fifth PIP, first to fifth MCP, thumb IP and thumb CMC joints.

All statistical analyses were performed using SPSS Statistics version 20.0 (IBM, Armonk, NY, USA). Mean values were compared using one-way analysis of variance or Student's *t*-test according to the number of groups compared, and proportions were compared using the chi-square test. For a 2×3 contingency table, significant differences (overall $P < 0.05$) were further analysed by pairwise comparisons.

Results

Characteristics of patients with anti-ARS antibodies and joint symptoms

The anti-ARS antibodies were found in 56 patients with hand X-ray available and included Jo-1 in 28, EJ in 9, OJ in 1, PL-7 in 7, PL-12 in 5 and KS in 6 patients. All of them had only anti-ARS antibody specificity without having any other myositis-specific antibodies. Their clinical diagnoses, aside from articular disorders, were polymyositis with or without interstitial lung disease (ILD) in 26 patients, DM with or without ILD in 10, ILD alone in 12, SSc in 5, SS in 1 and undifferentiated connective tissue disease in 2. At the time of X-ray evaluation, the mean age was 57.6 years, the mean disease duration from onset of joint symptoms was 9.4 years and 18 (32%), 25 (45%) and 16 (29%) patients were positive for ANA, RF and anti-CCP antibodies, respectively. We noted that the anti-ARS antibodies of 42 patients without joint symptoms were Jo-1 in 20 patients, EJ in 7, OJ in 2, PL-7 in 8, PL-12 in 4 and KS in 2 patients, and clinical diagnoses were PM in 18 patients, DM in 10, ILD alone in 9 and SSc in 5. There was no difference between patients with and without joint symptoms.

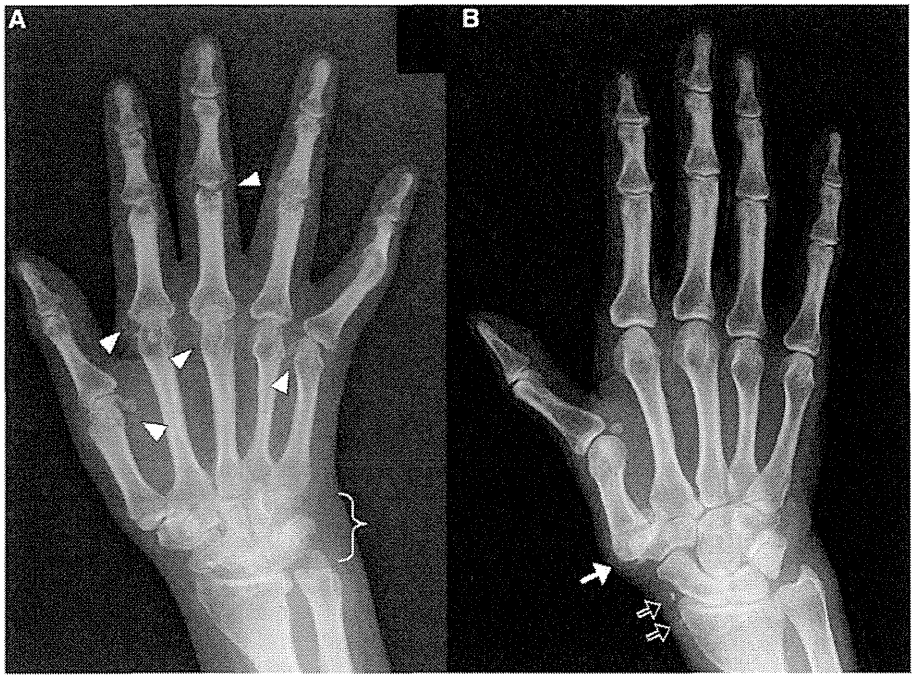
X-ray findings of the hands

Kappa coefficients of agreement between two X-ray readers were 0.93, 0.78 and 0.87 for erosion, subluxation and overall findings, respectively. Significant X-ray changes were found in 20 patients (36%). Erosions in the second to fifth DIP, second to fifth PIP, second to fifth MCP, first IP, first MCP and first CMC were found in similar frequencies, ranging from 12.5% to 23.2%. Subluxation in the first MCP was detected in 13 patients (23%), which was a higher rate of occurrence compared with other joints, including the second to fifth DIP, second to fifth PIP, second to fifth MCP, first IP and first CMC (9, 7, 11, 13 and 14%, respectively). Interestingly, some joints showed subluxations without erosions, and this finding was seen more frequently in the thumbs than in other joints (43% in the first IP, 38% in the first MCP and 13% in the first CMC compared with 0% in the second to fifth DIP, 25% in the second to fifth PIP and 0% in the second to fifth MCP). Nine patients (16%) had ankylosis of the wrist, while 3 (5%) had periarticular calcification.

Categorization based on hand X-ray findings

To evaluate potential correlations among individual X-ray findings in anti-ARS-positive patients, we examined correlations between individual X-ray findings. Correlations between individual X-ray findings, including erosion, subluxation, ankylosis and periarticular calcinosis, in 15 joints were analysed using cluster analysis (supplementary Fig. S1, available at *Rheumatology* Online). As a result, the patterns of findings largely fell into two major

FIG. 1 Representative hand X-rays of Jo-1-positive patients with (**A**) co-morbid RA and (**B**) a specific arthropathy



(**A**) Ankylosis was seen in the wrist (curly brace) and MCP and PIP joints were severely erosive (triangle). (**B**) Subluxation of the CMC joint of the thumb (closed arrow) and calcification on the wrist (open arrow) were visible.

groups: one showed chiefly erosions and ankylosis (group A) and the other showed principally subluxations (group B). Representative X-rays from these patterns are shown in Fig. 1. While ankylosis and erosions in the second to fifth MCPs were significantly associated with each other, both existed almost exclusively without subluxations in the first CMC. Only one patient had all these features together, and was regarded as group A in the analysis. As a result, 12 (21%) and 8 (14%) patients were categorized in groups A and B, respectively, while the remaining patients without significant X-ray findings were categorized in group N. As expected, X-ray findings in groups A and B differed significantly in erosions in the second to fifth PIPs and MCPs and ankylosis of the wrists, all of which were typically found in group A ($P < 0.01$ for all comparisons), while subluxation in the first CMC and periarticular calcification were characteristics of patients in group B ($P < 0.01$ and $P = 0.02$, respectively) (supplementary Table S1, available at *Rheumatology* online). The first CMC subluxation could be affected by CMC degenerative arthritis, but there was no correlation between subluxation and erosive changes on the first CMC erosions.

We next compared the demographic features and autoantibody profiles between groups stratified by X-ray findings (Table 1). Groups A and B had significantly longer disease duration compared with group N. All of the patients in group B had inflammatory myositis. All three patients with periarticular calcification were diagnosed as having PM or DM without overlapping features of SSc. The rates of positive RF and anti-CCP were significantly higher in group A, but the frequencies of positives were comparable between groups B and N. In contrast, all patients in group B were positive for anti-Jo-1 antibodies, and this frequency (100%) was significantly higher than in the other groups.

Discussion

Our study suggests that hand X-ray findings in patients with anti-ARS antibodies are heterogeneous and can be categorized into three groups. As found in a previous report [5], non-destructive arthropathy was most common. There were also two distinct groups of destructive arthropathies. Group A patients had erosions in the PIP and MCP joints and/or ankylosis of the wrists with anti-CCP and RF, while group B patients had subluxations of the CMC joint of the thumbs and periarticular calcification independent of anti-CCP or RF. The former type was found in patients with any anti-ARS specificity, while the latter group was exclusive to patients with anti-Jo-1 antibodies. Anti-CCP and RF are serological markers included in the new classification criteria for RA [9], which typically involves the PIP and MCP joints and causes ankylosis of the wrists. Moreover, the features of arthropathy in patients with the anti-Jo-1 antibody were reported to be dislocation of thumb joints and periarticular calcification [2–4]. Taken together, the

TABLE 1 Patient characteristics and X-ray findings between groups

	Group N ($n=36$)	Group A ($n=12$)	Group B ($n=8$)	Overall P-value
Age, mean (S.D.), years	55.3 (12.1)	62.8 (9.1)	60.1 (17.9)	0.18
Disease duration, mean (S.D.), years	6.4 (7.0)	13.6 (6.5)	16.4 (8.3)	<0.01[a]
Female, *n* (%)	25 (70)	10 (83)	8 (100)	0.26
Anti-Jo-1, *n* (%)	17 (48)	3 (25)	8 (100)	<0.01[b]
RF, *n* (%)	12 (33)	10 (83)	3 (38)	<0.01[c]
Anti-CCP, *n* (%)	6 (17)	9 (75)	1 (13)	<0.01[d]
ANA, *n* (%)	10 (28)	5 (42)	3 (38)	0.64
Inflammatory myopathy, *n* (%)	22 (61)	6 (50)	8 (100)	<0.01[e]
ILD alone, *n* (%)	9 (25)	3 (25)	0 (0)	0.20
DM skin lesion, *n* (%)	9 (25)	0 (0)	1 (13)	0.27
Fever, *n* (%)	3 (8)	0 (0)	0 (0)	0.18
RP, *n* (%)	7 (19)	4 (33)	2 (25)	0.13
Mechanic's hand, *n* (%)	6 (17)	1 (8)	2 (25)	0.13

Denominators are the total number of patients in each group. [a]$P<0.01$ and 0.01 between groups N and A, and between groups N and B, respectively. [b]$P<0.01$ for comparisons between groups N and B, and between groups A and B. [c]$P<0.01$ and 0.04 between groups N and A, and between groups A and B, respectively. [d]$P<0.01$ for comparisons between groups N and A, and between groups A and B. [e]$P=0.02$ for groups A and B.

measurements of RF, anti-CCP and anti-Jo-1 are useful in discriminating these two types of anti-ARS-associated destructive arthropathies.

The anti-CCP antibody is particularly valuable to diagnose RA due to its high specificity [10–12], and it is also known to be a marker for joint destruction since patients with RA with anti-CCP have more progressive joint destruction compared with those without [13, 14]. Nagashima *et al.* [6] reported two cases of DM with concomitant anti-Jo-1 and anti-CCP antibodies who presented with remarkable joint destruction in the hands, and this type of destructive arthropathy in patients with anti-Jo-1 may be a unique subtype. Cavagna *et al.* [7] examined 12 patients with anti-Jo-1 antibodies and suggested that anti-CCP is a marker of erosive arthritis in anti-ARS syndrome. Thus we could presume that arthropathy with erosions in the PIP and MCP joints and/or ankylosis of the wrists with anti-CCP and RF, which is observed in some patients with anti-ARS antibodies, is consistent with RA. Indeed, Nagashima *et al.* [15] reported later that the combination of inflammatory myositis and RA is not uncommon.

Since this is a cross-sectional study, in which all clinical information was obtained retrospectively, it is difficult to assess the natural history and therapeutic responses of anti-ARS-associated arthropathies. The disease duration of the patients with no remarkable X-ray findings was significantly shorter than those with RA and an arthropathy associated with an ARS. That leads us to consider that X-ray changes could increasingly emerge with time, especially in patients with anti-CCP and/or RF. However, the retrospective study design is the major limitation of this study and longitudinal analysis should be done in future prospective studies. One can speculate that the DIP erosion frequently found in anti-ARS-positive patients is explained by concomitant SpA, but it is unlikely because none of them had been clinically diagnosed as having AS, psoriasis or IBD or had inflammatory back pain or typical skin manifestations. However, we could not exclude this possibility because neither feet, knees or spine X-rays were available for those patients. Moreover, we classified the patients solely based on X-ray findings on bilateral hands. Another limitation of this study is that we could not appreciate the associations of distinctive X-ray findings with antibodies to non-Jo-1ARS due to the small sample size. In conclusion, serum autoantibody measurements are useful in classifying heterogeneous anti-ARS-associated arthropathies.

Rheumatology key messages

- Arthropathies with anti-aminoacyl tRNA synthetase (ARS) antibodies are heterogeneous in patterns of structural joint damage.
- There are two distinct destructive arthropathies of the hands: co-morbid RA and a specific arthropathy mainly affecting the thumbs.
- Autoantibody profiles, including anti-CCP, RF and individual anti-ARS specificity, are useful in classifying arthropathies.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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ORIGINAL ARTICLE

Drug free REmission/low disease activity after cessation of tocilizumab (Actemra) Monotherapy (DREAM) study

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Received: 27 September 2011 / Accepted: 15 April 2013

Abstract

Objectives To investigate the duration of remission and low disease activity (LDA) after cessation of tocilizumab (TCZ) treatment in rheumatoid arthritis patients who showed remission or LDA as assessed by DAS28 in response to preceding TCZ monotherapy, and to explore the factors contributing to prolonged efficacy duration.

Methods Disease activity was monitored for 56 weeks. The rate of continued efficacy was estimated by Kaplan–Meier curves.

Results A total of 187 patients were eligible. At baseline of this study, median disease duration was 7.8 years, preceding TCZ treatment period was 4.0 years and DAS28 was 1.5. The rate of continued LDA at 52 weeks was 13.4 % according to the Kaplan–Meier estimate. 19 patients (10 %) were completely drug-free and 17 patients (9.1 %) fulfilled DAS28 remission at 52 weeks. Multivariate Cox regression analysis identified low serum IL-6 and normalisation of MMP-3 levels at cessation of TCZ as independent predictive markers for longer duration of LDA. In patients with low serum IL-6 (<12.9 pg/mL) and

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normal MMP-3 levels, the rate of continued LDA reached 38.0 % at 52 weeks.
Conclusions TCZ monotherapy may induce biologics-free remission or LDA without concomitant use of synthetic DMARDs. Serum levels of IL-6 and MMP-3 are useful markers for identifying patients who could discontinue TCZ without acute disease flare.

Keywords Tocilizumab · Rheumatoid arthritis · Duration of efficacy · Drug free · Interleukin 6 · Matrix metalloproteinase 3

Introduction

Newly licensed medications, especially biological agents, have enabled the attainment of unprecedented outcomes for patients with rheumatoid arthritis (RA) [1–4], and structured patient management aiming to achieve remission is an achievable goal in many patients in clinical trials and in actual clinical practice [5–8]. However, because biologics are more expensive than conventional synthetic DMARDs, continuous therapy with biologics strains medical finances; the next step in research on the treatment of RA should be to evaluate the possibility of sustaining remission without the use of biologics.

Tocilizumab (TCZ) is a humanised anti-human IL-6 receptor (IL-6R) monoclonal antibody that inhibits IL-6 binding to IL-6R [9]. TCZ as monotherapy and in combination with methotrexate (MTX) has been demonstrated to frequently induce remission according to the 28-joint disease activity score (DAS28)-erythrocyte sedimentation rate (ESR) and also to prevent joint damage [10–20].

In a previous study, we showed that the degree of abnormality of serum IL-6 levels in RA patients was positively correlated with RA disease activity, and that serum IL-6 levels were decreased in patients who sustained DAS28 remission by TCZ monotherapy [21, 22]. This evidence suggests that TCZ may be able to be discontinued without acute flare of disease activity in patients whose serum IL-6 has normalised. Based on this assumption, we planned an open-labelled, single-arm, multicentre clinical trial to investigate *D*rug-free *RE*mission/low disease activity (LDA) after cessation of tocilizumab (*A*ctemra as a product name) *M*onotherapy (DREAM study) in RA patients.

Method

Patients

Eligible patients were those who had participated in previous long-term clinical studies of TCZ monotherapy conducted in Japan, and the inclusion criteria and study design for each of these studies have already been reported [23]. Briefly, eligible patients were ≥20 years of age and fulfilled the 1987 American Rheumatism Association criteria for RA[24] with a disease history of 6 months or longer (with the exception of the SAMURAI study [14], in which the eligible disease duration was restricted to between 6 months and 5 years). All subjects failed to respond satisfactorily to treatment with at least one DMARD, including MTX or immunosuppressants. At enrolment in the initial trials, the patients had active RA, defined as the presence of six or more swollen joints and six or more tender joints. Patients receiving corticosteroids

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(≤10 mg/day as prednisolone equivalent) and/or non-steroidal anti-inflammatory drugs (NSAIDs) were eligible if the dose had not increased during the 1-month washout period. Sexually active premenopausal women were required to have a negative urine pregnancy test at entry and periodically thereafter and to use effective contraception during the study period.

All patients were registered in this study within 4 weeks of the last observation in each preceding long-term extension study of TCZ monotherapy. Patients were enrolled if their DAS28-ESR was <2.6 at two or three of three consecutive assessment points, including the last observation point in the preceding study. Patients with DAS28-ESR ≤3.2 at two or three of three consecutive assessment points were additionally enrolled to know if the disease activity at TCZ discontinuation might influence the duration of DAS28 remission or LDA. Patients were excluded if they had received DMARDs, immunosuppressants, oral corticosteroids in excess of the dose at the initial infusion of TCZ, intravenous or intramuscular injections of corticosteroids, or plasmapheresis before being enrolled in this study. The baseline for each enrolled patient was defined as the time of the last TCZ infusion in the preceding clinical trial.

Study protocol

The study protocol was approved by the Ministry of Health, Labour and Welfare of Japan, and by the local ethical committees. All patients gave their written informed consent. This study is registered with http://clinicaltrials.gov/ (NCT00661284).

The primary endpoint of this study was the rate of DAS28 remission (DAS28-ESR <2.6) or LDA (DAS28-ESR ≤3.2) at 52 weeks after cessation of TCZ monotherapy, which was estimated from Kaplan–Meier curves prepared with the duration of continued efficacy for each patient defined as the time from the last infusion of TCZ in the preceding clinical study until loss of efficacy.

Nineteen hospitals in Japan participated in this study. Disease activities were monitored every 4 weeks for 56 weeks after cessation of TCZ for RA disease activity. During the study period, concomitant uses of NSAIDs and oral corticosteroid were allowed if the doses were not increased. Intra-articular injections of corticosteroids and hyaluronate preparations were avoided as far as possible, but surgical treatments were not limited. Additional RA treatments, including DMARDs, increases in oral corticosteroid dose, intravenous or intramuscular injections of corticosteroids, or plasmapheresis, were not allowed throughout the discontinuation period. Criteria for loss of efficacy was defined as DAS28-ESR >3.2 at two consecutive observations, initiation of additional RA treatments including increase in oral corticosteroid dose, the patient's request for retreatment, or the treating physician judging that retreatment was necessary. If patients met the criteria for loss of efficacy, observations in the study period were terminated.

Statistical analysis

Patients who had maintained a DAS28-ESR ≤3.2 at the last observation point in this study were handled as censored at that time. DAS28 remission and the 2011 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) remission criteria (Boolean approach) were also considered [25].

The rate of continued efficacy at each time point was also estimated from Kaplan–Meier curves. The factors contributing to the duration of efficacy were estimated from univariate and multivariate Cox regression analyses using the following patient background data for this study: age, gender, disease duration, American College of Rheumatology functional class, RA stage determined by Steinbrocker's criteria, corticosteroid dose, rheumatoid factor (RF), DAS28-ESR, modified health assessment questionnaire (MHAQ) score, serum IL-6 concentration, and serum matrix metalloproteinase (MMP)-3 concentration. The receiver operating characteristic (ROC) curve was used to determine the most sensitive and specific cut-off value for the serum IL-6 level. Ineligible patients were excluded from efficacy evaluations.

Results

Characteristics of patients

We enrolled 189 patients and 187 of them were eligible. The two patients who did not meet DAS28-ESR LDA at the last observation of preceding long-term extension studies were excluded from this study from 189 patients. At the baseline of this study, the median disease duration was 7.8 years and the median preceding TCZ treatment period was 4.0 years (min–max = 1.9–8.6 years). Of the patients, 126 (67.4 %) received TCZ with 8 mg/kg every 4 weeks before enrolling in this study, 45 (24.1 %) extended the treatment interval (39.7 ± 10.9 days, mean ± SD) and 3 reduced the TCZ dosage (2 for 4 mg/kg; 1 for 6 mg/kg every 4 week), mostly due to sufficient efficacy, while 13 patients (7.0 %) shortened the interval (10 for patient's convenience; 3 for insufficient efficacy).

Oral corticosteroids were being taken by 64 patients (34.2 %), with a mean dose of 2.8 mg/day for those patients; 143 patients (76.5 %) had no swollen joints; 137 patients (73.3 %) had no tender joints; 115 patients (61.5 %) had no swollen and no tender joints. The medina serum IL-6 concentration and serum MMP-3 concentration were also decreased at enrolment in this study compared

Table 1 Demographic and clinical characteristics of patients at baseline

Total of 187 patients	Before first TCZ infusion (baseline of previous studies)	At cessation of TCZ treatment (baseline of this study)
Age, years (range)	52 (21–75)	57 (26–78)
Gender, female (%)	164 (87.7)	164 (87.7)
Disease duration, years	3.1 (0.4–20.9)	7.8 (3.7–24)
Functional class[a], 1:2:3:4	16:154:17:0	91:94:2:0
RA stage[a], I:II:III:IV	9:90:48:40	13:76:40:58
Number of prior use of DMARDs	2 (1–9)	
Corticosteroid dose, mg/d	5 (0–15.0)	0 (0–7.0)
No of patients who used MTX previously (%)	169 (90.4)	
RF positive, RF ≥20 IU/mL (%)	160 (85.6)	No data
TCZ treatment period (years)		4.0 (1.9–8.6)
DAS28-ESR	6.2 (2.2–8.8)	1.5 (0–3.2)
Tender joint count (28-joint count)	9 (0–28)	0 (0–7)
Swollen joint count (28-joint count)	9 (0–26)	0 (0–6)
CRP, mg/dL	3.29 (0.3–20.1)	0.02 (0–5.2)
ESR, mm/h	57 (11–165)	5 (1–28)
MHAQ score	0.6 (0–2.0)	0 (0–1.4)
IL-6, pg/mL	32 (1.6–611)	19 (3.3–431)
MMP-3, ng/mL	346 (38–800)	55 (23–697)

Values are median (range) except where indicated otherwise

RA rheumatoid arthritis, *RF* rheumatoid factor, *DAS28* 28-joint disease activity score, *ESR* erythrocyte sedimentation rate, *MHAQ* modified health assessment questionnaire, *IL-6* interleukin 6, *MMP-3* matrix metalloproteinase 3

[a] RA functional status determined by the American College of Rheumatology criteria. RA stage determined by Steinbrocker's criteria

with the patient background before starting the TCZ treatment (Table 1). At enrolment in this study, 169 (90.4 %) met DAS28 remission, and 107 (57.2 %) met Boolean remission. The DAS28 remission and LDA were kept more than 24 weeks in 133 patients (71.1 %) and 159 patients (85.0 %), respectively, before enrolment into this study.

Continuation rate of DAS28 remission and LDA efficacy after cessation of TCZ treatment

The rate of continued efficacy LDA without concomitant use of synthetic DMARDs was 35.1 % [95 % confidence interval (CI) 28.2–42.0 %] at 24 weeks and 13.4 % (95 % CI 8.4–18.3 %) at 52 weeks according to the Kaplan–Meier estimate (Fig. 1). DAS28 remission and 2011 ACR/EULAR remission criteria (Boolean approach) were maintained in 17 patients (9.1 %) and 14 patients (7.5 %), respectively, at 52 weeks. Furthermore, efficacy continued throughout the study period without concomitant use of corticosteroids or NSAIDs during the study period in 19 patients (10.2 %). The mean DAS28-ESR of these 19 patients was 2.2 at week 52.

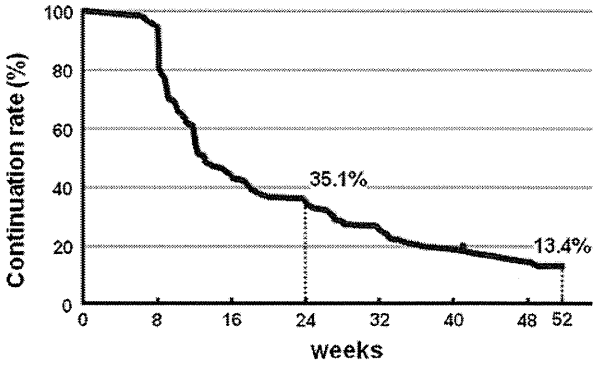

Fig. 1 Rate of continued LDA after cessation of tocilizumab treatment estimated by Kaplan–Meier method over 52 weeks

When we estimated the LDA continuation rates by the Kaplan–Meier method in the patients with DAS28 remission and new stringent Boolean-based remission at the cessation of TCZ, LDA continuation rates (95 % CI) at 52 weeks were 14.2 % (8.9–19.5 %) and 16.1 % (9.1–23.1 %), respectively. Further analysis for the factors contributing to the prolongation of efficacy duration is described later.

In total, 161 patients were withdrawn from this study. The major reason for the loss of efficacy was DAS28-ESR >3.2 at two consecutive visits in 44.7 % of patients (72/161 patients) and investigator's judgment in 39.8 % of patients (64/161 patients). The major reason of investigator's judgement was DAS28-ESR >3.2 at one visit in 84.4 % of patients (54/64 patients). However, there were no patients in whom disease activity flared up at the end of the observational period. Only 6.8 % (11/161 patients) were patients' request.

In terms of disease activity at cessation of TCZ monotherapy, the patients who completed the 52 weeks of this study period were comparable to the patients who withdrew from the study and restarted anti-rheumatic therapy before 52 weeks (Table 2).The serum IL-6 levels at baseline in the patients who restarted anti-rheumatic therapy before 52 weeks were higher than those in the patients who completed the 52-week study period [19.3 (range 0.7–431.0) pg/mL vs 10.9 (range 0.9–32.6) pg/mL]. In addition, the percentage of patients whose MMP-3 levels