*Table 6.* Effect of concomitant DMARD at baseline on clinical response during treatment with etanercept. "No" refers to patients without concomitant use of any DMARD.

| Baseline Variables | Comparison | OR | 95% CI | p |
|---|---|---|---|---|
| Remission model for all subjects* | | | | |
| Concomitant DMARD use at baseline | | | | |
| | MTX vs no | 1.36 | 1.16–1.60 | < 0.001 |
| | SSZ vs no‡ | 1.03 | 0.76–1.39 | 0.844 |
| | BUC vs no‡ | 1.24 | 0.90–1.69 | 0.186 |
| | Other DMARD vs no | 0.95 | 0.70–1.29 | 0.719 |
| Remission model for subjects treated with etanercept and MTX* | | | | |
| Concomitant MTX dose (mg/week) at baseline | | | | |
| | > 8 vs > 0 to ≤ 4 | 1.47 | 1.07–2.00 | 0.016 |
| | > 6 to ≤ 8 vs > 0 to ≤ 4 | 1.27 | 1.01–1.60 | 0.038 |
| | > 4 to ≤ 6 vs > 0 to ≤ 4 | 1.07 | 0.85–1.35 | 0.583 |
| Good response model for subjects treated with etanercept and MTX§ | | | | |
| Concomitant MTX dose (mg/week) at baseline | | | | |
| | > 8 vs > 0 to ≤ 4 | 1.53 | 1.17–2.00 | 0.002 |
| | > 6 to ≤ 8 vs > 0 to ≤ 4 | 1.16 | 0.95–1.40 | 0.141 |
| | > 4 to ≤ 6 vs > 0 to ≤ 4 | 1.11 | 0.91–1.35 | 0.294 |

* Of 7325 patients with data available for effectiveness analysis, multivariate analysis was performed on 6823 patients; 501 patients were excluded owing to lack of disease duration data, and 1 patient was excluded owing to lack of Steinbrocker class data. Of 6823 total patients, 1273 (18.7%) experienced remission. ‡ Concomitant SSZ refers to patients who were treated with etanercept plus SSZ with or without other DMARD (ETN + SSZ). Concomitant BUC refers to patients who were treated with etanercept plus BUC with or without other DMARD except SSZ (ETN + BUC). § Of 4146 patients who used concomitant MTX in effectiveness analysis population, multivariate analysis was performed on 3842 patients; 304 patients were excluded owing to lack of disease duration data, and/or lack of Steinbrocker class data. Of 3842 total patients, 810 (21.1%) experienced remission. Predictor analyses were undertaken using logistic regression models. In all models, results were adjusted for age, sex, Steinbrocker class, disease duration, previous use of infliximab, and baseline DAS28. BUC: bucillamine; DAS28: 28-joint Disease Activity Score; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; SSZ: sulfasalazine.

ETN + DMARD group. Superiority of etanercept plus MTX compared with etanercept monotherapy in our study is consistent with the results from previously reported clinical trials[4,6]. Because the background characteristics of the patients, which may affect effectiveness of ETN, were significantly different among the 3 groups, we adjusted for age, sex, Steinbrocker class, disease duration, previous use of infliximab, and baseline DAS28 and showed favorable effect of MTX to achieve better clinical response (Table 6).

Numerous clinical trials have demonstrated that aggressive combination therapy early in the course of RA may result in higher rates of clinical remission and less radiographic progression than monotherapy, conventional sequential therapy, or step-up therapy[4,18,19,20,21,22,23]. In our study, the remission rate was significantly greater with etanercept plus MTX than with etanercept alone.

Further, a positive correlation was suggested between MTX dosage and a favorable clinical outcome. Results of the Cox proportional hazards model indicated that patients receiving higher dosages of MTX had a higher probability of achieving clinical remission. Similar results were also reported in another study[24]. In addition, higher dosages of MTX did not alter the risk for SAE or SI, even though the dosage was > 8 mg weekly. These findings are especially noteworthy because MTX dosages are typically lower in Japan than in Western countries, where dosages of 15 to 20 mg weekly are often used[9]; relatively few of the patients in this Japanese study received MTX > 8 mg weekly. Yamanaka, *et al* reported that there was a positive correlation between MTX dosage and the frequency of adverse reactions with MTX in the IORRA cohort[9]. It was previously reported from the Japanese REAL cohort that the use of MTX > 8 mg weekly was a risk factor for SI[25]. In February 2011, the higher dosage of up to 16 mg weekly was approved by PMDA in Japan. Further investigations are expected in exploring safety and effectiveness of MTX at this higher dose in the Japanese population.

Although the DAS28 remission rate observed in the ETN + MTX group in our study (21%; data not shown) was lower than that observed in other clinical studies (35%)[6], the favorable risk/benefit ratio observed with combination etanercept plus MTX suggests that this approach is warranted in many patients with RA who can tolerate MTX. Indeed, aggressive combination regimens offer a high level of effectiveness and tolerability, which will make remission a realistic goal in many patients with RA[26].

Our study provided unique results in the clinical use of lower dosages of MTX with etanercept. Because MTX is

usually prescribed at more than 8 mg weekly in many countries but not in Japan, results for the lower dosage of MTX have not been well documented. Therefore, comparing safety and effectiveness between ≤ 8 mg weekly and > 8 mg weekly MTX plus etanercept is applicable to real-world MTX use of etanercept in Japan. This was consistent with the result of the JESMR study[27]. In that study, ≤ 8 mg weekly MTX plus etanercept was superior to etanercept monotherapy for inadequate responders to MTX.

Our results indicated that concomitant use of SSZ or BUC did not alter the risk for SAE and SI (Cox proportional hazard model; data not shown), and concomitant use of SSZ or BUC did not affect the remission rates (multiple logistic regression model). Combe, *et al* reported that concomitant use of SSZ with etanercept did not alter the incidence of AE, but the incidence of infection was significantly lower with combination therapy[28]. Regarding efficacy, etanercept plus SSZ was significantly more sustainable and efficacious for DAS improvement after 68 weeks of treatment compared with etanercept monotherapy[28]. In the Combe, *et al* study, duration of treatment was 2 years and the dosages of SSZ were 2, 2.5, and 3 g daily, which are higher than the typical dosage of SSZ (1 g daily) in Japan[28,29,30,31]. Shorter treatment duration and/or lower dosage of SSZ in our PMS study may explain this discrepancy. Regarding BUC, a DMARD approved only in Japan and Korea[31,32], evidence supporting its concomitant use with etanercept has not been established. Only the safety and efficacy of concomitant use of etanercept plus SSZ plus BUC has been reported[33]. In that study, the efficacy of concomitant use of etanercept plus SSZ or BUC was higher than that of etanercept monotherapy and comparable to that of etanercept plus MTX. Further studies are needed to evaluate the safety and effectiveness of concomitant use of these DMARD with etanercept.

As in our previous report[10], the main limitation of our current study was the absence of a comparator group and presence of indication bias for concomitant DMARD. PMS studies do not always include a comparator group, which makes it difficult to distinguish outcomes relating to ETN + MTX treatment from those caused by confounding factors. Another important limitation was that about 50% of patients were excluded from effectiveness analysis because of a lack of DAS28 data at baseline and/or Week 24. This exclusion makes it difficult to generalize the outcomes of effectiveness. The short duration of the 6-month PMS study was also an important limitation. Although most of the previously reported AE were detected and a general safety profile of etanercept was obtained, AE that require a longer followup period, such as malignancy, can hardly be evaluated. For this reason, we have conducted another longterm PMS study to evaluate AE, including malignancy. The results of this longterm study will be reported soon.

We used the MTX weekly dose at baseline to evaluate the influence on effectiveness without considering changes of dosage during the treatment period. The analysis with mean dosage of MTX may be necessary. In addition, radiographic findings were not included and the observational period was relatively short (6 months). There are also some limitations on statistical methodology. For Table 1, we have not considered the issue of multiple testing, so it is possible that the significant difference in some demographic and baseline disease characteristics will disappear when the correction is used. Despite these limitations, this all-cases, 2-year PMS study demonstrates the real-world safety and effectiveness of etanercept-DMARD combination therapy with data from about 14,000 patients.

Both etanercept monotherapy and etanercept in combination with DMARD are effective in improving RA disease control and are reasonably well tolerated. However, the best responses were observed in patients who received etanercept in combination with MTX, especially in those who received doses of MTX higher than those typically used in Japan. Our findings support the use of this treatment approach to improve RA control, establishing remission as a realistic goal for many patients.

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BRIEF REPORT

# Reduction of plasma IL-6 but not TNF-α by methotrexate in patients with early rheumatoid arthritis: a potential biomarker for radiographic progression

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**Abstract**
*Objective* To determine the effect of methotrexate (MTX) on plasma levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-α and to investigate their associations with clinical and radiographic responses in patients with early rheumatoid arthritis (RA).
*Methods* Sixty-two untreated RA patients with the disease duration of ≤36 months in whom MTX was initiated were consecutively identified in our prospective RA cohort and included in this study. Concomitant use of prednisolone and synthetic disease-modifying anti-rheumatic drugs with MTX was allowed, but patients who used biological agents were excluded. Plasma IL-6 and TNF-α levels were measured at the time of diagnosis (baseline) and 1 year later. The relationships of the clinical and radiographic data with plasma levels of IL-6 and TNF-α were analyzed.
*Results* The median age of the patients was 57 years, 49 patients were female, and the median disease duration was 3 months. Forty-six (74.2 %) patients were anti-cyclic citrullinated protein antibody-positive. Serum C-reactive protein (CRP), plasma IL-6, and DAS28 decreased significantly ($p$ <0.001) after MTX treatment, but plasma TNF-α did not. Radiographic progression was significantly correlated with disease activity score and plasma IL-6 levels but not with CRP or TNF-α after MTX treatment. Patients with plasma IL-6 level above 4.03 pg/ml showed clinically relevant radiographic progression with a sensitivity of 91.7 % and a specificity of 88.0 %.
*Conclusion* In this early RA cohort, we demonstrated a significant ($p$ <0.001) reduction of plasma IL-6, but not TNF-α, during MTX treatment. The post-treatment IL-6 level was a strong indicator of radiographic progression.

**Keywords** Interleukin-6 · Methotrexate · Rheumatoid arthritis · Tumor necrosis factor-alpha

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## Introduction

Methotrexate (MTX) is the anchor drug in the treatment of rheumatoid arthritis (RA), and its effectiveness is well established [1]. However, it is still unclear how MTX affects the complicated cytokine network involved in the pathology of RA [2, 3], and few studies have investigated changes in plasma cytokine levels during MTX treatment [4].

Tumor necrosis factor (TNF)-α and interleukin (IL)-6 play central roles in the pathogenesis of RA and are the main targets of biological agents [5]. MTX inhibits cytokine production induced by T cell activation in vitro [6, 7]. However, there are no reports regarding the effects of MTX on circulating cytokine levels in treatment-naive early RA patients. We performed longitudinal measurements of plasma TNF-α and IL-6 in patients in such a cohort and analyzed the relationship between cytokine levels and clinical effectiveness and radiographic progression.

## Patients and methods

### Patients

Systematic Cohort Analysis in Keio University–Rheumatoid Arthritis (SAKURA) is a prospective cohort consisting of 150 consecutive newly diagnosed RA patients at Keio University Hospital between August 2008 and March 2011. At inclusion in SAKURA, those patients had never been treated

with any disease-modifying antirheumatic drugs (DMARDs) or corticosteroids, and each rheumatologist in charge started treatment. Since some patients in SAKURA had already severe joint destruction with a long history of arthralgia at the time of diagnosis, we selected patients with disease duration (which we defined here as a time period from symptom onset to diagnosis) of up to 36 months in this current study in order to catch small changes in joint destruction. Concomitant use of classic DMARDs or low-dose prednisolone at a dose of no more than 10 mg/day was allowed. Clinical, radiographic, and plasma cytokine data was collected at baseline and 1 year later. Since the interval of the patient's visit was 1–3 months, 1-year data was obtained with 3-month allowance. Patients in whom a biological agent was started within 1 year were analyzed with data just before the commencement of it using last observation carried forward (LOCF) method. Although the time points of data collection at baseline were not necessarily exactly the same with the time of the MTX commencement, all the patients had been treated with MTX for more than 5 months during this study. Six patients assessed at 16 to 18 months due to patient's personal reasons were exceptionally included. This study was approved by the ethics committee at Keio University School of Medicine. Written informed consent was obtained from all patients.

### Clinical and radiological assessments

Clinical characteristics including matrix metalloproteinase-3 (MMP-3) which was routinely measured in our clinics were obtained from the medical charts. Radiographs of the hands and feet were taken at baseline and 1 year later (at the same time as the blood samples). Two blinded and independent readers (NN and YK) scored the images using the van der Heijde modified Total Sharp Score (mTSS) [8]. The smallest detectable change of the two in mTSS was 1.32. The mean of the two scores was used in the analysis. Estimated yearly progression of mTSS (ΔmTSS/year) was adjusted by the exact months from baseline to the second time of x-ray.

### Plasma assays

Plasma samples were collected at baseline and 1 year later. All samples were stored immediately after collection at −30 °C in our laboratory. Plasma TNF-α and IL-6 levels were assessed using chemiluminescent enzyme immunoassays (R&D Systems Inc., Minneapolis, MN, USA) that had a threshold of detection of 0.55 and 0.30 pg/ml, respectively. The details of the measurement methods were reported previously [9].

### Statistical analysis

Continuous data are presented as the median with interquartile range (IQR), mean with standard deviation, or as a number with percentage value as appropriate. The Wilcoxon signed rank test was used to examine changes between baseline and 1 year later. Correlation of two continuous variables was analyzed using Pearson's correlation. Receiver operating characteristics (ROC) curve analysis was used to evaluate the performance of the indices as a method for identifying clinically relevant radiographic progression (CRRP), defined as ΔmTSS/year >3 [10]. Multivariate analysis was performed using multiple regression models by parameters with $p$ value <0.20 in preceding univariate analysis. All statistical analyses were performed with JMP 9 (SAS Institute Inc., Cary, NC, USA).

**Table 1** Baseline characteristics and treatments during this study of rheumatoid arthritis patients ($n$=62)

| | |
|---|---|
| Female, $n$ (%) | 49 (79.0) |
| Age, years; median (IQR) | 57 (49–66) |
| Mean ± SD | 56±14.5 |
| Disease duration, months; median (IQR) | 3 (2–7) |
| Mean ± SD | 6.3±8.0 |
| Serologic status, $n$ (%) | |
| RF+/anti-CCP+ | 43 (69.4) |
| RF+/anti-CCP- | 3 (4.8) |
| RF-/anti-CCP+ | 3 (4.8) |
| RF-/anti-CCP- | 13 (21.0) |
| Steinbrocker Stage, I/II/III/IV, $n$ | 51/9/0/2 |
| MTX use during this study, $n$ (%) | 62 (100) |
| dosage, mg/week; median (IQR) | 8 (8–10) |
| dosage, mg/week; mean ± SD | 8.7±2.3 |
| Concomitant PSL use during this study, $n$ (%) | 6 (9.8) |
| Concomitant DMARD use during this study, $n$ (%) | |
| BUC | 6 (9.8) |
| SSZ | 6 (9.8) |
| BUC and SSZ | 1 (1.6) |
| TAC | 1 (1.6) |

Results are expressed as median (IQR), mean ± SD, or number (%) as appropriate

*BUC* bucillamine, *CCP* cyclic citrullinated protein, *DMARD* disease-modifying antirheumatic drug, *MTX* methotrexate, *PSL* prednisolone, *RF* rheumatoid factor, *SSZ* salazosulfapyridine; *TAC* tacrolimus

## Results

### Patient characteristics

Sixty-two patients were analyzed. Of the SAKURA cohort, 88 patients were excluded because of one of the following reasons: disease duration >36 months, a biological agent was started within 5 months, MTX was not used, or lost to follow-up. The median duration of observation was 11 (7–14) months. The median age was 57 (49–66) years, 49 (79.0 %) patients

were female, and the median disease duration was 3 (2–7) months. Patient characteristics and the treatment during this study are shown in Table 1. Nineteen (31 %) patients did not have 1-year data because of the commencement of a biologic agent or patient's personal reasons and their data were analyzed using LOCF methods.

## Clinical assessments

The median Disease Activity Score 28 (DAS28) and the Health Assessment Questionnaire–Disability Index (HAQ-DI) significantly ($p$ <0.001) decreased from baseline to 1 year later from 4.42 to 2.58 and from 0.625 to 0.125, respectively (Table 2). Changes in other parameters are shown in Table 2. Despite the clinical effectiveness of MTX, the mTSS showed a statistically significant increase ($p$ <0.001) from 4 (0.75–8.25) to 7 (2–11.25). CRRP was observed in 12 (19.4 %) patients. Median ΔmTSS/year was 0.5 (0–2.5). Thirty-one (50 %) patients showed no radiographic progression (ΔmTSS/year <0.5).

## Plasma cytokine concentrations

Plasma IL-6 and TNF-α were detectable in 59 (95.2 %) and 36 (58.1 %) patients at baseline, respectively, and in 57 (91.9 %) and 37 (59.7 %) patients 1 year later, respectively. The median plasma IL-6 level decreased from 4.72 to 1.04 pg/ml ($p$ <0.001), while there was no significant difference in the level of TNF-α at baseline and 1 year later (0.87 and 0.83 pg/ml, respectively; $p$=0.14) (Table 2).

## Association of radiographic progression with clinical parameters

The ΔmTSS/year correlated with DAS28 ($r$=0.469, $p$ <0.01); simplified disease activity index (SDAI) ($r$=0.422, $p$ <0.0006); MMP-3 ($r$=0.581, $p$ <0.01); and IL-6 ($r$=0.673, $p$ <0.01). However, it did not correlate with C-reactive protein (CRP); ($r$=0.221, $p$=0.08) or with TNF-α ($r$=0.158, $p$=0.22) (Fig. 1a–f). Plasma IL-6 level at 1 year discriminated between patients with CRRP and those without CRRP at a cut-off level of 4.03 pg/ml with a sensitivity of 91.7 % and a specificity of 88.0 %, while plasma TNF-α level at 1 year did not (Fig. 1k and l). DAS28, SDAI, CRP, and MMP-3 discriminated between these groups but less effectively than IL-6 (areas under the ROC curve were 0.810, 0.813, 0.792, and 0.675, respectively; Fig. 1g–j). We also performed the ROC analyses in the same way on the Sharp units of 0.5, 2, and 5 instead of 3 (CRRP), and got the almost same results (data not shown). The proportion of patients with CRRP paralleled with specified categories of disease activity or with parameter values, except for TNF-α (Fig. 1m–r). Moreover, we divided the patients by their DAS28 at 1 year into "remission and low disease activity (LDA)" group and "moderate disease activity (MDA) and high

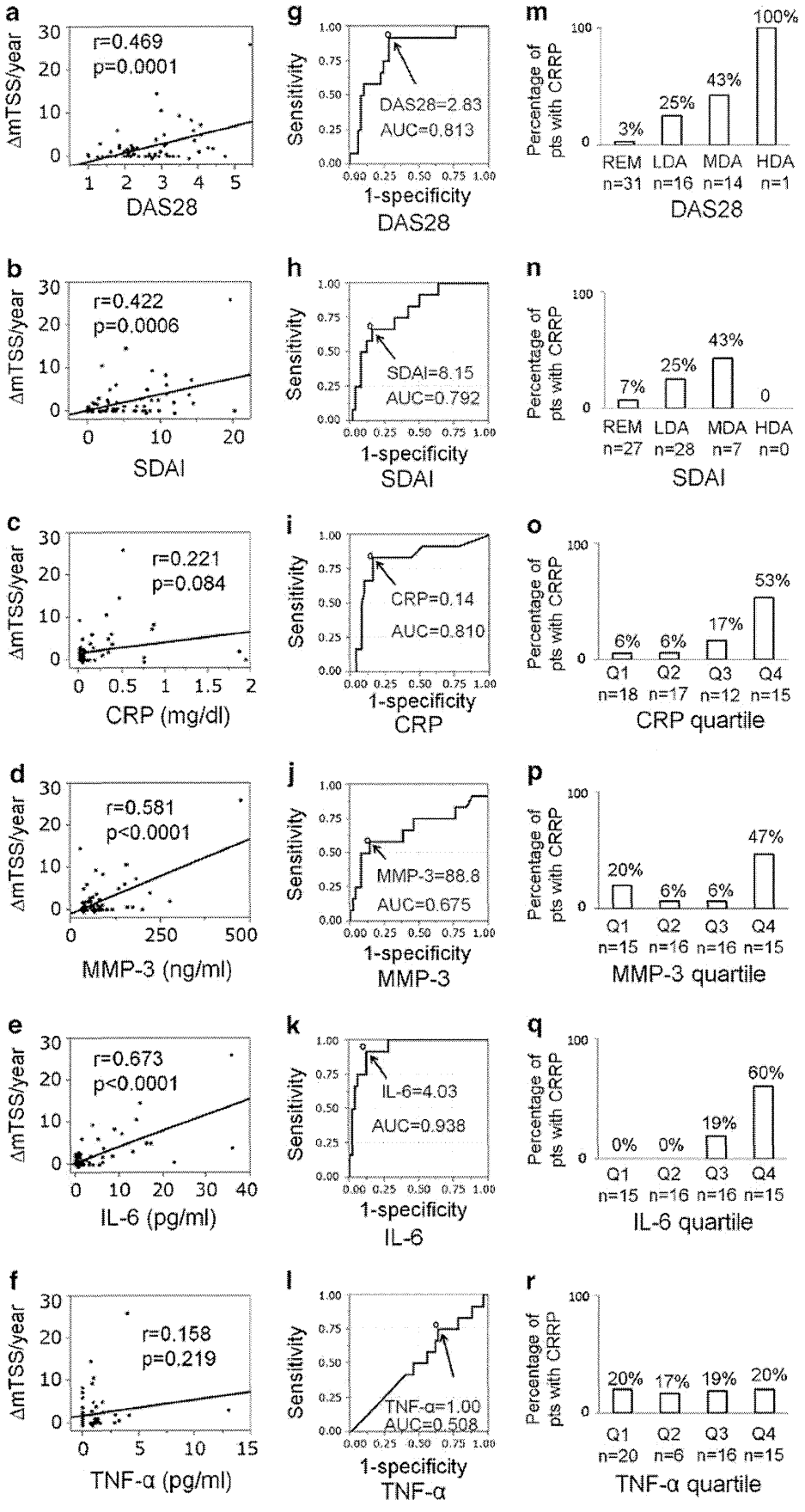
**Table 2** Comparison of the clinical and biological characteristics of early rheumatoid arthritis patients at baseline and 1 year later

| | Baseline | 1 year | $p$ Value |
|---|---|---|---|
| DAS28 | 4.42 (3.60–5.62) | 2.58 (1.93–3.16) | <0.001* |
| HDA, *n* (%) | 21 (33.9) | 1 (1.6) | – |
| MDA, *n* (%) | 35 (56.5) | 14 (22.6) | – |
| LDA, *n* (%) | 4 (6.5) | 16 (25.8) | – |
| REM, *n* (%) | 2 (3.2) | 31 (50.0) | – |
| SDAI | 16.2 (9.4–28.1) | 3.86 (1.66–8.24) | <0.001* |
| HDA, *n* (%) | 18 (29.0) | 0 (0) | – |
| MDA, *n* (%) | 23 (37.1) | 7 (11.3) | – |
| LDA, *n* (%) | 21 (33.9) | 28 (45.2) | – |
| REM, *n* (%) | 0 (0) | 27 (43.5) | – |
| SJC | 4 (2–9) | 0 (0–2) | <0.001* |
| TJC | 4 (1–8) | 0 (0–1.3) | <0.001* |
| PtGA (mm) | 38.5 (12–65) | 15 (5–33) | <0.001* |
| PhGA (mm) | 33.5 (25–51) | 6 (1–15) | <0.001* |
| ESR (mm/h) | 33 (20–68) | 14 (8–20.5) | <0.001* |
| CRP (mg/dl) | 0.55 (0.10–1.43) | 0.06 (0.02–0.18) | <0.001* |
| MMP-3 (ng/ml) | 87.4 (57.2–163.7) | 69.9 (46.1–87.0) | <0.001* |
| HAQ-DI | 0.625 (0.344–1.156) | 0.125 (0–0.625) | <0.001* |
| mTSS | 4 (0.75–8.25) | 7 (2–11.25) | <0.001* |
| IL-6 (pg/ml) | 4.72 (2–11.55) | 1.04 (0.58–5.41) | <0.001* |
| TNF-α (pg/ml) | 0.87 (<0.55–1.58) | 0.83 (<0.55–1.18) | 0.14 |

Results are expressed as median (IQR) or number (%) as appropriate. The Wilcoxon signed rank test was used to compare the variables

*CRP* C-reactive protein, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *HAQ-DI* health assessment questionnaire-disability index, *HDA* high disease activity, *IL* interleukin, *LDA* low disease activity, *MDA* moderate disease activity, *MMP* matrix metalloproteinase, *mTSS* modified Total Sharp Score, *PhGA* physician global assessment, *PtGA* patient global assessment, *REM* remission, *SDAI* simplified disease activity index, *SJC* swollen joint count, *TNF* tumor necrosis factor, *TJC* tender joint count

*$p$ <0.05 when compared with baseline value


a
ΔmTSS/year
r=0.469
p=0.0001
DAS28
g
Sensitivity
DAS28=2.83
AUC=0.813
1-specificity
DAS28
m
Percentage of pts with CRRP
3%
25%
43%
100%
REM LDA MDA HDA
n=31 n=16 n=14 n=1
DAS28
b
ΔmTSS/year
r=0.422
p=0.0006
SDAI
h
Sensitivity
SDAI=8.15
AUC=0.792
1-specificity
SDAI
n
Percentage of pts with CRRP
7%
25%
43%
0
REM LDA MDA HDA
n=27 n=28 n=7 n=0
SDAI
c
ΔmTSS/year
r=0.221
p=0.084
CRP (mg/dl)
i
Sensitivity
CRP=0.14
AUC=0.810
1-specificity
CRP
o
Percentage of pts with CRRP
6%
6%
17%
53%
Q1 Q2 Q3 Q4
n=18 n=17 n=12 n=15
CRP quartile
d
ΔmTSS/year
r=0.581
p<0.0001
MMP-3 (ng/ml)
j
Sensitivity
MMP-3=88.8
AUC=0.675
1-specificity
MMP-3
p
Percentage of pts with CRRP
20%
6%
6%
47%
Q1 Q2 Q3 Q4
n=15 n=16 n=16 n=15
MMP-3 quartile
e
ΔmTSS/year
r=0.673
p<0.0001
IL-6 (pg/ml)
k
Sensitivity
IL-6=4.03
AUC=0.938
1-specificity
IL-6
q
Percentage of pts with CRRP
0%
0%
19%
60%
Q1 Q2 Q3 Q4
n=15 n=16 n=16 n=15
IL-6 quartile
f
ΔmTSS/year
r=0.158
p=0.219
TNF-α (pg/ml)
l
Sensitivity
TNF-α=1.00
AUC=0.508
1-specificity
TNF-α
r
Percentage of pts with CRRP
20%
17%
19%
20%
Q1 Q2 Q3 Q4
n=20 n=6 n=16 n=15
TNF-α quartile

◀ **Fig. 1** Association of disease activity and biomarkers after methotrexate (MTX) treatment with radiographic progression in early rheumatoid arthritis patients. Association of **a** DAS28, **b** SDAI, **c** CRP, **d** MMP-3, **e** IL-6, and **f** TNF-α with ΔmTSS/year. The ROC curve discriminated between ΔmTSS/year >3 (CRRP) and ΔmTSS/year ≤3 for **g** DAS28, **h** SDAI, **i** CRP, **j** MMP-3, **k** IL-6, and **l** TNF-α. The percentage of patients who had CRRP according to disease activity category: **m** DAS28 and **n** SDAI or quartiles of **o** CRP, **p** MMP-3, **q** IL-6, and **r** TNF-α. *CRP* C-reactive protein; *CRRP* clinically relevant radiographic progression; *DAS* disease activity score; *HDA* high disease activity; *IL* interleukin; *LDA* low disease activity; *MDA* moderate disease activity; *MMP* matrix metalloproteinase; *pts* patients; *Q* quartile; *REM* remission; *ROC* receiver operating characteristics; *SDAI* simplified disease activity index; *TNF* tumor necrosis factor; ΔmTSS/year, estimated yearly progression of modified Total Sharp Score

disease activity (HDA)" group, and examined the association between cytokines and radiographic changes. While in remission and LDA group, patients with the high IL-6 level were disposed to show CRRP, in MDA and HDA group no patients with low IL-6 level showed CRRP. In regard to TNF-α, we could not find any relationships (data not shown).

### Baseline characteristics for prediction of RA patients with radiographic progression

Among the parameters, sex and the plasma level of TNF-α at baseline were statistically significant ($p$ <0.05) but weakly correlated with ΔmTSS/year in multivariate analysis (Table 3). Thus, female patients with higher plasma TNF-α level at baseline may be predisposed to worse radiographic progression.

## Discussion

This study demonstrated that in early RA patients, the plasma IL-6 level significantly decreased during MTX treatment, while the plasma TNF-α level did not change. Radiographic progression correlated with higher levels of plasma IL-6 after MTX treatment, suggesting that inhibition of plasma IL-6 may be critical for preventing radiographic progression.

Most of the patients analyzed in this study were in the early stages of RA and had mild to moderate disease activity. Although the overall clinical response to MTX was excellent, one-fifth of the patients exhibited CRRP, which is one of the criteria that typically prompt consideration of treatment changes [10]. In fact, there was a significant correlation between the DAS28 score at 1 year and radiographic progression. However, it should be noted that one-fourth of the patients with LDA resulted in CRRP according to DAS28 category. In this regard, the plasma IL-6 level after MTX treatment showed the strongest association with radiographic progression. For these patients, the measurement of plasma IL-6 might be able to provide additional clinical information that we may as well consider the treatment strategy more carefully in those patients with plasma IL-6 levels greater than 4.03 pg/ml to suppress joint destruction even if they were in remission or LDA.

MTX appeared to have a greater effect in terms of suppressing circulating IL-6 than on suppressing circulating TNF-α. It is likely that the effect of MTX on cytokines in RA is achieved mainly via inhibition of IL-6 production. In this context, it makes sense that TNF inhibitors have a greater effect when used in combination with MTX than when used as monotherapy [11] which is not the case with the IL-6 receptor inhibitor tocilizumab [12, 13]. Moreover, the result that the patients with higher TNF-α at baseline showed worse radiographic progression indicated that TNF-α could be used as a biomarker to consider the treatment strategy. Since our study showed that MTX have little effect on TNF-α, we may be able to suggest that anti-TNF agents be an option at an early stage in patients with high TNF-α.

**Table 3** Association of baseline parameters of early rheumatoid arthritis patients with ΔmTSS/year

| | Univariate analysis | | Multivariate analysis |
|---|---|---|---|
| | $r$ value | $p$ value | $p$ value |
| Age | 0.099 | 0.44 | – |
| Sex | 0.220 | 0.09 | 0.03* |
| Disease duration | 0.096 | 0.46 | – |
| Seropositivity | 0.171 | 0.18 | 0.98 |
| Erosions | 0.084 | 0.52 | – |
| MTX dosage | 0.085 | 0.51 | – |
| DAS28 | 0.059 | 0.65 | – |
| SDAI | 0.012 | 0.92 | – |
| SJC | 0.002 | 0.99 | – |
| TJC | 0.060 | 0.65 | – |
| PtGA | 0.085 | 0.51 | – |
| PhGA | 0.117 | 0.37 | – |
| ESR | 0.220 | 0.09 | 0.32 |
| CRP | 0.008 | 0.95 | – |
| MMP-3 | 0.006 | 0.97 | – |
| HAQ-DI | 0.004 | 0.98 | – |
| IL-6 | 0.049 | 0.70 | – |
| TNF-α | 0.472 | 0.0001 | 0.0006* |

Pearson's correlation coefficient ($r$ value) and $p$ value are shown. Dichotomous variables (i.e., sex, seropositivity, and erosion) were scored as 0 or 1:0, male, seronegative, or the absence of initial erosion; 1, female, seropositive, or the presence of initial erosion. Baseline markers with $p$ values less than 0.20 in univariate analysis were analyzed in multivariate analysis.

*$p$ <0.05

*ΔmTSS/year* estimated yearly progression of modified Total Sharp Score, *CRP* C-reactive protein, *DAS* disease activity score, *HAQ-DI* health assessment questionnaire-disability index, *IL* interleukin, *ESR* erythrocyte sedimentation rate, *MMP* matrix metalloproteinase, *PhGA* physician global assessment, *PtGA* patient global assessment, *SDAI* simplified disease activity index, *SJC* swollen joint count, *TJC* tender joint count, *TNF* tumor necrosis factor

Our study has several limitations. First, since the study population was small, the results of this study may not be valid for all RA patients. For example, the results showing that IL-6 was affected by MTX might be different if the patients showed an inadequate response to MTX. Second, we examined only two cytokines. Since multiple cytokines are involved in the pathogenesis of RA [14], other cytokines need to be investigated as well. Third, the patients showed a good response to MTX when a lower dose of MTX was used rather than the global recommended dose [15]. Ethnic differences between Caucasians and Japanese might account for the difference in the effectiveness of MTX.

In conclusion, this study is the first to demonstrate that MTX reduces IL-6 but not TNF-α in vivo and to show that the plasma IL-6 concentration after MTX was the parameter that was most associated with radiographic progression. Further investigations in a larger population are needed to confirm these findings.

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ORIGINAL ARTICLE

# No increased mortality in patients with rheumatoid arthritis treated with biologics: results from the biologics register of six rheumatology institutes in Japan

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**Abstract**
*Objective* To investigate the influence of biologics on mortality and risk factors for death in rheumatoid arthritis (RA) patients.
*Methods* RA patients treated with at least one dose of biologics in daily practice in six large rheumatology institutes ("biologics cohort") were observed until 15 May 2010 or death, whichever occurred first. Mortality of the biologics cohort and the "comparator cohort" (comprising patients among the IORRA cohort who had never been treated with biologics) was compared to that of the Japanese general population. Factors associated with mortality were assessed by a Cox model.
*Results* Among 2683 patients with 6913.0 patient-years of observation, 38 deaths were identified in the biologics cohort. The probability of death in patients lost to follow-up, calculated using the weighted standardized mortality ratio (SMR), was 1.08 [95 % confidence interval (CI) 0.77–1.47] in the biologics cohort and 1.28 (95 % CI 1.17–1.41) in the comparator cohort. Pulmonary involvement was the main cause of death (47.4 %), and the disease-specific SMR of pneumonia was 4.19 (95 % CI 1.81–8.25). Risk factors for death included male gender [hazard ratio (HR) 2.78 (95 % CI 1.24–6.22)], advanced age (HR 1.07, 95 % CI 1.03–1.11), and corticosteroid dose (HR 1.08, 95 % CI 1.01–1.17).
*Conclusion* Mortality in RA patients exposed to biologics did not exceed that in patients not exposed to biologics, but death from pulmonary manifestations was proportionally increased in RA patients exposed to biologics.

**Keywords** Biologics · Cause of death · Mortality · Rheumatoid arthritis · Standardized mortality ratio

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## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that results in worsening physical function and extra-articular manifestations. Due to these manifestations, patients with RA have been reported to experience excessive mortality in Western countries [1–6]. Comparably worse mortality has recently been reported for Japanese patients with RA [7]. However, the cause of death differs

greatly between Western and Japanese RA patients [7]. The main cause of death in Western RA patients is cardiovascular disease (CVD), comprising 40–50 % of deaths. In contrast, one-quarter of Japanese RA patients die from malignancy and respiratory disease, respectively, with pneumonia and interstitial lung disease being the two equivalent primary causes of respiratory disease [7].

Many studies have reported favorable results of biologic treatment of RA in decreasing disease activity, preventing bone destruction, and suppressing CVD events and death [8–11], and possibly improving overall mortality [8, 12, 13] in Western RA patients. However, several reports have demonstrated that use of anti-tumor necrosis factor (TNF) therapy is associated with an increased risk of serious infection, especially in the first six months of treatment [14, 15]. Considering that previous reports [7, 16–18] indicate that the causes of death of Japanese RA patients differ from those of Western RA patients, it is yet to be clarified whether biologic treatment results in the same benefit to Japanese RA patients as that reported for Western RA patients.

We conducted this study to elucidate whether treatment of RA with biologics actually provides an improvement in the mortality of Japanese RA patients and to assess causes of death and risk factors for death in a multicenter observational cohort study.

## Patients and methods

### Study design

All of the patients with RA who had been treated with at least one dose of a biologic (including infliximab, etanercept, tocilizumab and adalimumab) in daily clinical practice were listed in six rheumatology centers, and these patients were registered into the "biologics cohort" at the start of this observational study in September 2008. Additional new RA patients who were treated with at least one dose of these biologics after September 2008 were introduced into this biologics cohort and both were observed until 15 May 2010 or until death, whichever came first. A query about their survival was sent to the patients who were lost to follow-up at the end of this observational period by the relevant physician. This study was conducted through the cooperation of six large rheumatology centers in Japan: the Institute of Rheumatology of Tokyo Women's Medical University, the Department of Rheumatology and Clinical Immunology of Saitama Medical Center in Saitama Medical University, the First Department of Internal Medicine of the University of Occupational and Environmental Health, Japan, the Department of Orthopedic Surgery and Rheumatology of Nagoya University, the Department of Diabetes, Endocrinology and Rheumatology of Japanese Red Cross Kyoto Daiichi Hospital, and the Division of Rheumatology and Clinical Immunology of Jichi Medical University. This study was conducted after approval was given by the ethical committee at each institute. The use of biologics in daily practice was judged by responsible rheumatologists, with reference to the guideline for the introduction of biologics in practice developed by the Japanese College of Rheumatology.

### Assessments

The baseline data of the patients who had received a biologic agent (infliximab, etanercept, tocilizumab, or adalimumab) were collected, including age, sex, disease duration, concomitant methotrexate (MTX) use and dose, concomitant corticosteroid use and dose (converted into the equivalent prednisolone dose) at the initiation of the corresponding biologic, and when and which biologic agent was introduced. Medical history, including tuberculosis, malignancy, CVD, cerebrovascular disease, and gastrointestinal bleeding was reported. Disease activity was assessed by either DAS28 or DAS28-CRP [19] according to their utilization at each institute. Physical function was also measured either by Health Assessment Questionnaire (HAQ), the Japanese version of the HAQ (J-HAQ) [20], or the modified HAQ (M-HAQ). When the biologic agent was discontinued, the time and reason for discontinuation were reported. In cases where the patient had switched biologics, the biologics used during the observational period were recorded. Patients who received at least one dose of a biologic were followed up even if they discontinued the agent or switched to an alternative biologic agent. At the end of this study, on 15 May 2010, the survival of each patient was confirmed as accurately as possible, as described below. Causes of death were collected from each institute and classified according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).

The primary outcome measure in this study was mortality. The notification of death and the cause of death were acquired from the relevant physician at each rheumatology institute. When the patient's survival was uncertain at the end of this study period, a letter to confirm their survival was sent by the affiliated institute. When the death of the patient was approved, cause of death and time were reported.

### Comparison cohorts

Patients with RA who were enrolled in the IORRA (Institute of Rheumatology, Rheumatoid Arthritis) cohort after April 2003 (around which time the first biologic agent

became available in daily practice in Japan) and who had never been treated with any biologics until 15 May 2010 were included in the "comparison cohort" (nonbiologics IORRA) in this study. IORRA is a large observational cohort established in 2000 at the Institute of Rheumatology, Tokyo Women's Medical University, with the primary aim being to assess standard RA outcomes in accordance with the current treatments used in daily practice, as reported precisely previously [7, 21, 22]. The IORRA cohort basically comprises all RA patients who attended the Institute of Rheumatology, Tokyo Women's Medical University, and fulfilled the classification criteria of the American College of Rheumatology for RA [23] in principle after informed consent was obtained. The IORRA survey is conducted biannually (in April and May and in October and November). Disease activity evaluated by DAS28 [19], physical function evaluated by J-HAQ [20], and laboratory data used in daily practice were collected. Medications, including disease-modifying antirheumatic drugs (DMARDs), MTX, corticosteroids, and biologics used within the previous six months were also reported. Active follow-up by mail was conducted for patients who did not attend the subsequent IORRA survey. The cause and the time of the death were collected from the physicians at the affiliated hospitals, from residual family members through active follow-up inquiry by mail, and from the police when it was sudden or accidental.

## Statistical analysis

### *Mortality*

The mortality of patients in this biologics cohort was compared to the mortality of the Japanese general population reported by Japanese Health and Wealth (http://www.stat.go.jp/data/nihon/02.htm) via standardized mortality ratios (SMRs) and confidence intervals (95 % CIs). Standardization was conducted by the calendar year of recruitment, gender, and age. Since this biologics cohort study was observational, patients were not completely followed unless an active effort was made to capture their survival status. Nonresponse to mailed queries is a potential source of bias in this type of research survey. Thus, to assess mortality, we attempted to statistically analyze it as follows. First, we assumed that all patients who were lost to follow-up at the end of the observation period were alive; the SMR was then calculated and compared to the Japanese general population (analysis 1). Second, we assumed that patients who were ascertained to be alive at three months (analysis 2) or six months (analysis 3) before the end of the observation period were alive at the end of the observational period; these data were compared to those of the Japanese general population. Finally, as Kauppi et al. [24] reported that patients with RA who did not respond to mailed queries were 1.65 times more likely to have died over the two-year follow-up period compared to responders, we statistically determined that patients who were lost to follow-up would have died at this rate (analysis 4), and these data were compared to those of the Japanese population.

The mortality of the patients in the comparison cohort (non-biologics IORRA) was analyzed using SMR with the same weighting as in analysis 4, assuming the patients who were lost to follow-up were 1.65 times more likely to have died over the two-year follow-up period than the Japanese general population (analysis 5).

### *Causes of death and disease-specific mortality*

The causes of death in this biologics cohort were collected and cause-specific mortality was analyzed for malignancy, pneumonia, and respiratory diseases including pneumonia. Death within three months of the last use of biologics was considered "death on biologics." For patients who were ascertained to have died due to a specific cause of death, the disease-specific mortality rate and SMR were calculated by comparing to the mortality of the Japanese general population reported by Japanese Health and Wealth (http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suii01/deth10.html).

### *Risk factors for mortality*

To assess the risk factors for mortality among patients who had been exposed to at least one dose of a biologic, variables including sex, age (year), body mass index (BMI) ($kg/m^2$), disease duration (year), disease activity (DAS28), MTX dose (mg/week), and corticosteroid dose (mg/day) at the initiation of the first biologics were analyzed using a Cox model.

## Results

Overall, 2683 patients with RA who had been exposed to biologics were registered into the biologics cohort. The first biologics used in these patients included infliximab ($n = 1112$, 41.2 %), etanercept ($n = 1053$, 39.0 %), adalimumab ($n = 345$, 12.8 %), tocilizumab ($n = 173$, 6.4 %), and abatacept ($n = 4$, 0.1 %). The mean (SD) age was 56.0 (13.9) years, mean disease duration was 10.1 (10.1) years, and 84.0 % of patients were women (Table 1). Baseline disease activity was 5.6 (1.2) as evaluated by DAS28 or 4.9 (1.2) by DAS28-CRP. MTX and corticosteroids were concomitantly prescribed in 77.7 and 54.2 % of patients, respectively. Discontinuation of the

**Table 1** Baseline characteristics of the biologics cohort

| | Percentage or mean | SD |
|---|---|---|
| Female (%) | 84.0 | |
| Age (years) | 56.0 | 13.9 |
| Disease duration (years) | 10.1 | 10.1 |
| BMI (kg/m$^2$) | 21.5 | 3.4 |
| General VAS | 57.0 | 23.5 |
| Disease activity | | |
| DAS28 | 5.6 | 1.2 |
| DAS28-CRP | 4.9 | 1.2 |
| ESR (mm/h) | 54.9 | 30.2 |
| CRP (mg/dl) | 3.10 | 3.40 |
| RF (IU/ml) | 202.4 | 348.2 |
| Physical dysfunction (HAQ, J-HAQ, MHAQ) | 1.17 | 0.81 |
| EQ-5D | 0.62 | 0.13 |
| Past history | | |
| Pulmonary tuberculosis (%) | 3.4 | |
| Malignancies (%) | 4.5 | |
| Ischemic heart diseases (%) | 1.4 | |
| Cerebrovascular disease (%) | 1.3 | |
| GI bleeding (%) | 1.0 | |
| MTX use (%) | 77.7 | |
| MTX dose (mg/week) | 7.6 | 3.2 |
| Corticosteroid use (%) | 54.2 | |
| Prednisolone dose (mg/day) | 3.9 | 3.4 |

Data shown are the % or mean (standard deviation) values, as appropriate

*VAS* visual analogue scale, *DAS28* disease activity score 28, *ESR* erythrocyte sedimentation rate, *CRP* C reactive protein, *RF* rheumatoid factor, *HAQ* health assessment questionnaire, *EQ-5D* EuroQoL 5 dimension, *GI* gastrointestinal, *MTX* methotrexate

first biologic was reported in 36.1 % of patients. Reasons for discontinuation of biologics included great response (7.1 %), insufficient effect (38.6 %), side effects (19.8 %), and economic reasons (2.9 %). Among patients who discontinued their first biologic, 43.2 % of patients switched to a second biologic. During this observation period, 64.8 % of patients were treated with one biologic, 17.2 % were treated with two biologics, and 18.0 % were treated with three or more biologics.

### Mortality

Thirty-eight deaths were recorded among 6913.0 patient-years (1072.4 patient-years for males and 5840.6 patient-years for females) of observation in the biologics cohort, and 537 patients (20.0 %) were lost to follow-up. SMRs were calculated with several assumptions (Table 2). When assuming that all of the patients lost to follow-up were alive, the SMR of RA patients treated with biologics did not exceed that of the Japanese general population [analysis 1, SMR 1.02 (95 % CI 0.72–1.40)]. When assuming that the patients who were ascertained to be alive at three months (analysis 2) or six months (analysis 3) before the end of the observation period were alive, the assumed SMR for the general population was 2.17 (95 % CI 1.73–2.70) in analysis 2 and 1.96 (95 % CI 1.54–2.46) in analysis 3. Upon weighting for patients lost to follow-up at the end of the observation period using the 1.65 times death assumption (as described in "Patients and methods"), the SMR in this biologics cohort (analysis 4) was 1.08 (95 % CI 0.77–1.47) compared with that of the Japanese general population [1.45 (95 % CI 0.86–2.30) in males and 0.90 (95 % CI 0.57–1.35) in females].

When the same weighting for patients lost to follow-up was applied to the nonbiologics IORRA cohort, the assumed SMR was 1.28 (95 % CI 1.17–1.41) for all subjects [1.31 (95 % CI 1.11–1.53) for males and 1.27 (95 % CI 1.13–1.43) for females] as compared to the Japanese general population.

### Causes of death and cause-specific mortality

The most frequent cause of death was respiratory disease (47.4 %), including pneumonia (21.1 %) and interstitial lung disease (18.4 %), followed by infection other than pneumonia and malignancies (Table 3). When only deaths that occurred within three months of the last administration of biologics were considered, deaths from respiratory disease (58.8 %) including pneumonia (23.5 %) and interstitial pneumonia (23.5 %) were most prominent.

Concerning disease-specific mortality, deaths from malignancy in RA patients treated with biologics did not exceed those in the Japanese general population [malignancy-specific SMR, 0.30 (95 % CI 0.10–0.69)]; however, deaths from pneumonia (pneumonia-specific SMR 4.19, 95 % CI 1.81–8.25) and respiratory disease (respiratory-specific SMR 9.42, 95 % CI 5.58–14.88) were much higher than those in the Japanese general population (Table 4).

### Risk factors for mortality

Risk factors for mortality (analyzed by a Cox proportional hazards model) were male gender [hazard ratio (HR) 2.78 (95 % CI 1.24–6.22), $p < 0.05$], older age [HR 1.07 (95 % CI 1.03–1.11), $p < 0.001$], and corticosteroid dose [HR 1.08 (95 % CI 1.01–1.17), $p < 0.05$], as shown in Table 5.

## Discussion

This is the first study to deal with mortality in patients with RA treated with biologics in Japan. In general, the

**Table 2** Adjusted mortality rates and standardized mortality ratios (SMRs) of biologics-treated rheumatoid arthritis patients ("biologics cohort") and rheumatoid arthritis patients among the IORRA cohort who had never taken biologics ("nonbiologics IORRA cohort") as compared to the Japanese general population

| | Observed | Observation (patient-years) | Crude rate/100,000 patient-years | Adjusted mortality rate | | | SMR | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Per 100,000 patient-years | 95 % lower | 95 % upper | SMR | 95 % lower | 95 % upper |
| Analysis 1: biologics cohort (assuming that all patients who were lost to follow-up at the end of observation period are alive) | | | | | | | | | |
| Total | 38 | 6913.03 | 834.29 | 423.60 | 228.50 | 717.67 | 1.02 | 0.72 | 1.40 |
| Male | 17 | 1072.41 | 921.50 | 672.03 | 301.05 | 1292.97 | 1.40 | 0.81 | 2.24 |
| Female | 21 | 5840.62 | 751.05 | 186.49 | 93.43 | 332.87 | 0.84 | 0.52 | 1.28 |
| Analysis 2: biologics cohort (assuming that all patients who were ascertained to be alive at three months before the end of the observation period were alive) | | | | | | | | | |
| Total | 81 | 6913.03 | 834.29 | 700.08 | 470.12 | 1003.22 | 2.17 | 1.73 | 2.70 |
| Male | 23 | 1072.41 | 921.50 | 846.01 | 434.85 | 1483.29 | 1.89 | 1.20 | 2.84 |
| Female | 58 | 5840.62 | 751.05 | 560.79 | 393.21 | 775.65 | 2.31 | 1.76 | 2.99 |
| Analysis 3: biologics cohort (assuming that all patients who were ascertained to be alive at six months before the end of the observation period were alive) | | | | | | | | | |
| Total | 73 | 6913.03 | 834.29 | 628.58 | 406.84 | 927.81 | 1.96 | 1.54 | 2.46 |
| Male | 22 | 1072.41 | 921.50 | 821.43 | 414.13 | 1459.73 | 1.81 | 1.13 | 2.74 |
| Female | 51 | 5840.62 | 751.05 | 444.52 | 307.90 | 621.07 | 2.03 | 1.51 | 2.67 |
| Analysis 4: biologics cohort (assuming that patients who were lost to follow-up were 1.65 times more prone to die) | | | | | | | | | |
| Total | 40.20 | 6913.03 | 834.29 | 442.73 | 243.45 | 739.70 | 1.08 | 0.77 | 1.47 |
| Male | 17.65 | 1072.41 | 921.50 | 691.31 | 314.95 | 1315.47 | 1.45 | 0.86 | 2.30 |
| Female | 22.55 | 5840.62 | 751.05 | 205.47 | 102.56 | 367.66 | 0.90 | 0.57 | 1.35 |
| Analysis 5: nonbiologics IORRA cohort (assuming that patient who were lost to follow-up was 1.65 times more prone to die) | | | | | | | | | |
| Total | 445.86 | 39078.17 | 1140.94 | 743.37 | 628.64 | 872.98 | 1.28 | 1.17 | 1.41 |
| Male | 161.19 | 6775.95 | 2378.91 | 814.48 | 648.09 | 1010.55 | 1.31 | 1.11 | 1.53 |
| Female | 284.66 | 32302.21 | 881.25 | 675.50 | 522.91 | 858.72 | 1.27 | 1.13 | 1.43 |

investigation of mortality is conducted by accessing death certificates or death records provided by the government or local government. However, there is no national death database in Japan, and it is quite difficult to access death certificates, even from local governments. Thus, we attempted to register as many cases as possible from the institutes that participated in this study, and to monitor death information actively in each clinical environment. IORRA was used as an external control population, since the IORRA cohort is considered to be representative of Japanese RA patients in a real-world setting and is the only cohort in which mortality of RA patients has been analyzed and published [7]. In this study, we demonstrated that the mortality of Japanese RA patients treated with at least one dose of biologics in daily practice did not exceed that in the Japanese general population, whereas the mortality of patients among the IORRA cohort who had never been treated with biologics slightly exceeded that seen in the Japanese general population. Even though these two cohorts came from different populations, it is hoped that treatment with biologics may improve the mortality of patients who can be treated with biologics. This result is comparable to recent reports from Western countries [12, 13, 25]. In those countries, information on comorbidity, hospitalization, and death can be obtained from nationwide registries, making it possible to calculate mortality more accurately, even though patients lost to follow-up are not mentioned. In this study, the number of patients who were lost to follow-up was relatively large, so the sensitivity analysis need to be executed by using assumption according to the report of Kauppi et al. How best to manage patients who are lost to follow-up (which inevitably occurs in this type of study) is a major issue to be solved.

The result that patients who were treated with at least one dose of biologics have a better outcome needs to be interpreted carefully, because we compared SMRs from different sources. The potential for selection bias in this study should be considered. First of all, patients who were candidates for biologics treatment were expected to tolerate the biological therapy. Second, patients who receive biologics were carefully screened for occult infections, malignancies, and comorbidities such as respiratory diseases before treatment. Thirdly, they were also monitored more extensively during the treatment, so adverse events, including upper respiratory infections and malignancies,

were more likely to have been identified in the biologic cohort beforehand. However, this possible selection bias favoring less severe complications in the biologic cohort does not completely explain our results. Additional considerations include the fact that 25.9 % of patients discontinued biologics during the observation period, and the average 2.6 years of the observation performed in this study may not have been long enough to sufficiently evaluate mortality.

Respiratory diseases, primarily pneumonia and interstitial lung disease, were the predominant causes of death in this biologics cohort, followed by infections other than pneumonia, malignancy, and CVD. In Western countries, CVD is the major cause of death in the general population, and it affects a larger proportion of patients with RA. Biologics, mainly anti-TNF agents, are expected to reduce the incidence and risk of cardiovascular events and improve mortality [11, 26], but CVD is still the main cause of death in Western RA patients treated with biologics. In contrast, rates of respiratory diseases (especially pneumonia) in this biologics cohort were significantly high, and the disease-specific SMR for pneumonia was about four times higher than that of the Japanese general population. When we considered deaths limited to within three months of the last use of biologics, 58 % of these particular RA patients died from respiratory diseases, including pneumonia; in other words, pneumonia and respiratory diseases tended to occur while using biologics. Interstitial lung disease is one of the major causes of death in Japanese patients with RA, accounting for half of all cases of respiratory disease; this was also true in this biologics cohort. Recently, interstitial lung disease has been extensively discussed in the context

**Table 3** Causes of death classified according to ICD-10 chapter number in patients with rheumatoid arthritis treated with biologics

| Chapter | Blocks | Chapter title | Total deaths ($N = 38$), $n$ (%) | Death within three months after the last use of biologics ($N = 17$), $n$ (%) |
|---|---|---|---|---|
| I | A00–B99 | Certain infections and parasitic diseases | 6 (15.8) | 2 (11.8) |
| II | C00–D48 | Malignancies | 5 (13.2) | 2 (11.8) |
| IV | E00–E90 | Endocrine, nutritional and metabolic diseases | 1 (2.6) | |
| IX | I00–I99 | Diseases of the circulatory system | 5 (13.2) | 1 (5.9) |
| | I20–I25 | Ischemic heart diseases | 2 (5.3) | 1 (5.9) |
| | I60–I69 | Cerebrovascular diseases | 2 (5.3) | |
| X | J00–J99 | Diseases of the respiratory system | 18 (47.4) | 10 (58.8) |
| | J10–J18 | Influenza and pneumonia | 8 (21.1) | 4 (23.5) |
| | J99 | Rheumatoid lung disease | 7 (18.4) | 4 (23.5) |
| XVIII | R00–R99 | Symptoms, signs and abnormal clinical and laboratory findings not classified elsewhere | 3 (7.9) | 2 (11.8) |

*ICD-10* International Statistical Classification of Disease and Related Health Problems, Tenth Revision

**Table 4** Disease-specific mortalities and standardized mortality ratios (SMRs) of patients treated with at least one dose of biologics

| Observed | Patient-years | Adjusted mortality rate | Per 100,000 patient-years | 95 % CI | SMR | 95 % CI |
|---|---|---|---|---|---|---|
| Malignancies | | | | | | |
| Total | 5 | 6913.03 | 44.92 | 10.90–121.78 | 0.30 | 0.10–0.69 |
| Male | 2 | 1072.41 | 65.79 | 7.94–237.93 | 0.37 | 0.04–1.33 |
| Female | 3 | 5840.62 | 24.93 | 5.09–73.15 | 0.26 | 0.05–0.76 |
| Pneumonia | | | | | | |
| Total | 8 | 6913.03 | 189.42 | 62.16–439.46 | 4.19 | 1.81–8.25 |
| Male | 5 | 1072.41 | 317.29 | 82.41–832.08 | 6.82 | 2.21–15.91 |
| Female | 3 | 5840.62 | 66.96 | 5.81–270.49 | 2.55 | 0.52–7.44 |
| Respiratory diseases | | | | | | |
| Total | 18 | 6913.03 | 309.65 | 151.55–561.60 | 9.42 | 5.58–14.88 |
| Male | 9 | 1072.41 | 455.74 | 177.50–957.40 | 12.27 | 5.61–23.29 |
| Female | 9 | 5840.62 | 169.72 | 51.81–409.58 | 7.64 | 3.49–14.51 |

*SMR* standardized mortality ratio, *95 % CI* 95 % confidence intervals

**Table 5** The risk factors for death in patients with rheumatoid arthritis treated with at least one dose of biologics

| | Coefficient | HR | 95 % CI | *p* |
|---|---|---|---|---|
| Male sex | 1.021 | 2.78 | 1.24–6.22 | 0.013 |
| Age (years) | 0.068 | 1.07 | 1.03–1.11 | <0.001 |
| Disease duration (year) | −0.024 | 0.98 | 0.93–1.02 | 0.291 |
| DAS28 | −0.133 | 0.88 | 0.64–1.20 | 0.404 |
| Methotrexate dose (mg/week) | −0.042 | 0.96 | 0.87–1.06 | 0.389 |
| Steroid dose (mg/day) | 0.081 | 1.08 | 1.01–1.17 | 0.029 |

*HR* hazard ratio, *95 % CI* 95 % confidence interval, *DAS28* 28-joints disease activity score

of treatment with or without biologics [6, 27, 28]; thus, reducing the incidence and mortality of interstitial lung disease in this patient population is an important issue.

We have demonstrated that risks for mortality included age, male gender, and corticosteroid dose at the initiation of the first biologic in this biologics cohort. Jacobsson reported that disability, VAS for pain, and presence of comorbidity (COPD, diabetes, or CVD) were strong predictors of mortality according to time-dependent proportional hazards models. In this study, we could not perform time-dependent analysis because it was difficult to obtain all of the required data on physical function and VAS for pain. In addition, as we did not establish any central adjudicative committee for this study, each institution needed to authorize the recording of data on comorbidity and death. Thus, it was difficult to obtain that information in this study. However, we found that the dose of corticosteroids at the initiation of the first biologic was a risk factor for mortality. It is the consensus that the concomitant use of corticosteroids is a risk factor for mortality in patients with RA, even though corticosteroids are more likely to be prescribed to patients in whom immunosuppressants—including biologics—are not indicated due to comorbidities.

In conclusion, this study demonstrated that no increase in mortality was associated with the introduction of biologics during RA treatment in Japan. This important issue should be further studied through an improved methodology for assessing mortality, including access to death certificates.

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**Conflict of interest** A. Nakajima, K. Saito, E. Inoue, W. Fukuda, T. Yoshio, A. Taniguchi, S. Momohara: None. T. Kojima: Abbott Japan, Bristol–Myers Squibb, Chugai Pharmaceutical, Eisai, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer Japan, and Takeda Pharmaceutical. S. Minota: Takeda Pharmaceutical, Bristol–Myers, Chugai Pharmaceutical, Mitsubishi Tanabe. K. Amano: Abbott Japan, Chugai Pharmaceutical. N. Ishiguro has received speaking fees from Takeda Pharma, Mitsubishi Tanabe Pharma, Astellas Pharma, Chugai Pharma, Abbott Japan, Bristol–Myers Squibb, Eisai, Janssen Pharma, and Pfizer Japan. T. Takeuchi has received grants from Abbott Japan Co., Ltd., Astellas Pharma, Bristol–Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Nippon Shinyaku Co., Ltd., Otsuka Pharmaceutical, Pfizer Japan Inc., Sanofi–Aventis K.K., Santen Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Teijin Pharma Ltd., speaking fees from Abbott Japan Co., Ltd., Bristol–Myers K.K., Chugai Pharmaceutical Co,. Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., and Takeda Pharmaceutical Co., Ltd., and consultant fees from Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., and Asahi Kasei Medical K.K.Y. Tanaka has received consulting fees, speaking fees, and/or honoraria from Mitsubishi Tanabe Pharma, Abbott Japan, Chugai Pharma, Janssen Pharma, Eisai Pharma, Santen Pharma, Pfizer, Astellas Pharma, Daiichi Sankyo, GlaxoSmithKline, AstraZeneca, Otsuka Pharma, Actelion Pharma Japan, and Eli Lilly Japan, and has received research grant support from Bristol–Myers Squibb, MSD, Chugai Pharma, Mitsubishi Tanabe Pharma, Astellas Pharma, Abbott Japan, Eisai Pharma, and Janssen Pharma. H. Yamanaka has received speaking fees from Abbott Japan Co., Ltd., AstraZeneca K.K., Bristol–Myers Squibb, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, Otsuka Pharmaceutical Co., Ltd., Pfizer Japan Inc., Takeda Pharmaceutical Company Ltd., Teijin Pharma Limited, and UCB Japan Co. Ltd. The IORRA study is supported by 38 pharmaceutical companies: Asahikasei Kuraray Medical Co., Ltd., Abbott Japan Co., Ltd., Asahikasei Pharma Corporation, Astellas Pharma Inc., AstraZeneca K.K., Bristol–Myers Squibb, Chugai Pharmaceutical Co., Ltd., Daiichi Fine Chemical Co., Ltd., Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Eisai Co., Ltd., GlaxoSmithKline K.K., Hisamitsu Pharmaceutical Co., Inc., Janssen Pharmaceutical K.K., Japan Tobacco Inc., Kaken Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co. Ltd., Mitsubishi Chemical Medience Corporation, Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical Co., Ltd., MSD K.K., Mundipharma K.K., Nippon Chemiphar Co., Ltd., Nippon Shinyaku Co., Ltd., Novartis Pharma K.K., Otsuka Pharmaceutical Co., Ltd., Pfizer Japan Inc., Sanofi Aventis K.K., Santen Pharmaceutical Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Sekisui Medical Co., Ltd., Taishotoyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Ltd., Teijin Pharma Ltd., Torii Pharmaceutical Co., Ltd., UCB Japan Co. Ltd., and ZERIA Pharmaceutical Co., Ltd.

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OPEN ACCESS

EXTENDED REPORT

# 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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## ABSTRACT

**Objectives** To evaluate the efficacy and safety of adalimumab+methotrexate (MTX) in Japanese patients with early rheumatoid arthritis (RA) who had not previously received MTX or biologics.

**Methods** This randomised, double-blind, placebo-controlled, multicentre study evaluated adalimumab 40 mg every other week+MTX 6–8 mg every week versus MTX 6–8 mg every week alone for 26 weeks in patients with RA (≤2-year duration). The primary endpoint was inhibition of radiographic progression (change (Δ) from baseline in modified total Sharp score (mTSS)) at week 26.

**Results** A total of 171 patients received adalimumab+MTX (mean dose, 6.2±0.8 mg/week) and 163 patients received MTX alone (mean dose, 6.6±0.6 mg/week, p<0.001). The mean RA duration was 0.3 years and 315 (94.3%) had high disease activity (DAS28>5.1). Adalimumab+MTX significantly inhibited radiographic progression at week 26 versus MTX alone (ΔmTSS, 1.5±6.1 vs 2.4±3.2, respectively; p<0.001). Significantly more patients in the adalimumab+MTX group (62.0%) did not show radiographic progression (ΔmTSS≤0.5) versus the MTX alone group (35.4%; p<0.001). Patients treated with adalimumab+MTX were significantly more likely to achieve American College of Rheumatology responses and achieve clinical remission, using various definitions, at 26 weeks versus MTX alone. Combination therapy was well tolerated, and no new safety signals were observed.

**Conclusions** Adalimumab in combination with low-dose MTX was well tolerated and efficacious in suppressing radiographic progression and improving clinical outcomes in Japanese patients with early RA and high disease activity.

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that is associated with joint damage and progressive disability, an increased risk of morbidity related to comorbid conditions, and substantial socioeconomic costs.[1–3] Given the significant impact biologic therapies have had in the treatment of RA, a paradigm shift has emerged toward earlier inclusion of these therapies in the management of RA.[3 4] Furthermore, international guidelines published in 2010 recommend a treat-to-target goal of remission for patients with early RA in order to mitigate radiographic progression and long-term disability.[5] The efficacy and safety of adalimumab, a tumour necrosis factor (TNF)-α inhibitor, administered as monotherapy or in combination with methotrexate (MTX) for the treatment of RA has been well established in clinical trials conducted in Western countries.[6–12] In early RA, the PREMIER and OPTIMA studies demonstrated that initial combination therapy with adalimumab and MTX was superior to MTX alone in inhibiting radiographic progression and improving clinical symptoms.[6 7 12]

Translating efficacy and safety results of RA Western-based studies to an Eastern populace can be potentially misleading given the genetic, medical and environmental differences (eg, body weight) observed between the two populations.[13] A limited number of studies have evaluated the efficacy or effectiveness and safety of adalimumab in Japanese patients. However, these studies either assessed adalimumab monotherapy in moderate-to-severe RA[14] or were retrospective[15] or postmarketing surveillance studies[16] of adalimumab monotherapy or combination therapy in a population with a wide range of RA duration and prior biologic and MTX experience. Thus, a randomised, placebo-controlled study of adalimumab +MTX combination therapy in MTX-naive Japanese patients with early RA was lacking.

The current study, called adalimumab, a human anti-TNF monoclonal antibody, outcome study for the persistent efficacy under allocation to treatment strategies in early RA, or HOPEFUL 1, was conducted to compare the efficacy and safety of early intervention with adalimumab+MTX versus MTX alone for 26 weeks in inhibiting radiographic progression in MTX-naive Japanese patients with RA.

## PATIENTS AND METHODS

Patients aged ≥20 years were evaluated during March 2009 and November 2010 from 94 centres. Eligible patients had RA (1987-revised American College of Rheumatology (ACR) criteria),[17] of ≤2-year duration, a tender joint count ≥10, a swollen joint count ≥8, a C reactive protein (CRP) level ≥1.5 mg/dl or erythrocyte sedimentation rate

(ESR) ≥28 mm/h, and had ≥1 joint erosion or were rheumatoid factor positive. Patients had not previously received MTX, leflunomide or >2 other disease-modifying antirheumatic drugs (DMARDs). Patients who had previously received cyclophosphamide, cyclosporine, azathioprine, tacrolimus or biologic DMARDs (eg, anti-TNF-α therapy) and patients with a chronic infection, interstitial pneumonia, or a history of tuberculosis or malignancy were excluded from the study.

The phase III trial consisted of a randomised, double-blind, placebo-controlled, 26-week phase followed by a 26-week open-label extension phase (clinicaltrials.gov identifier, NCT00870467; only 26-week double-blind data presented). After a 4-week washout period for patients taking eligible DMARDs and a >2-week screening period for all patients, participants were randomised (1 : 1) to receive subcutaneous adalimumab 40 mg or placebo every other week, both administered in combination with oral MTX 6–8 mg/week (adalimumab +MTX vs MTX alone) for 26 weeks. Treatment with MTX was initiated at 6 mg/week and increased to 8 mg/week in patients who did not experience ≥20% decrease from baseline in tender or swollen joint counts on or after week 8, unless investigators indicated a safety concern. In addition, reduction of the MTX dose to 4 mg/week was permitted at the investigator's discretion. All patients received concomitant oral folic acid 5 mg/week. Patients who experienced a >20% increase from baseline in tender and swollen joint counts at weeks 12, 16 or 20 were to discontinue blinded treatment with adalimumab or placebo and were eligible for open-label rescue treatment with adalimumab 40 mg every other week.

The primary endpoint was inhibition of radiographic progression assessed as the change from baseline (Δ) in modified total Sharp score (mTSS) at week 26. All single-emulsion radiographs of the hands (posteroanterior view) and feet (anteroposterior view) obtained from a patient were scored by two independent readers blinded to patient and treatment, as previously described,[6] with the exception that the triquetrum/pisiform joint was not scored for erosions and the first interphalangeal joint was not scored for joint-space narrowing (range, 0–380) (see online supplementary text for more information).

Secondary efficacy endpoints included ACR responses[18 19] by visit; clinical remission (the 28-joint disease activity score with ESR (DAS28-ESR)<2.6) at week 26;[20 21] and change from baseline in the Health Assessment Questionnaire disability index (HAQ-DI)[22] at week 26. Several additional post hoc analyses were conducted, including assessments of the DAS28-CRP, simplified disease activity index (SDAI)[23] and clinical disease activity index (CDAI) scores[24] over time; clinically relevant radiographic progression (ΔmTSS>3); European League Against Rheumatism responses[25] at week 26; and clinical remission, defined as DAS28-CRP<2.6,[26] SDAI≤3.3,[27 28] CDAI≤2.8[28] or meeting Boolean remission criteria,[27] at week 26. Low, medium and high disease activity was also determined using DAS28-ESR, DAS28-CRP, SDAI and CDAI. Adverse events (AEs) and clinical laboratory parameters were routinely monitored during the study. A 28-day follow-up after the completion of or discontinuation from the study and a 70-day follow-up after the last dose of adalimumab administration were conducted to evaluate safety.

## Statistics

The primary endpoint was analysed using the Wilcoxon rank sum test for observed data with a separate supportive analysis using linear extrapolation (LE) to impute missing values. Secondary endpoints were analysed using the Fisher's exact test and Wilcoxon rank sum test for discrete variables and continuous variables, respectively. Non-responder imputation was used for binary variables, and the last-observation-carried-forward approach was applied for continuous variables. The safety population included all randomised patients who received ≥1 dose of study medication and had ≥1 efficacy assessment.

To identify baseline predictors of no radiographic progression (mTSS≤0.5) and clinical remission (DAS28-ESR<2.6),

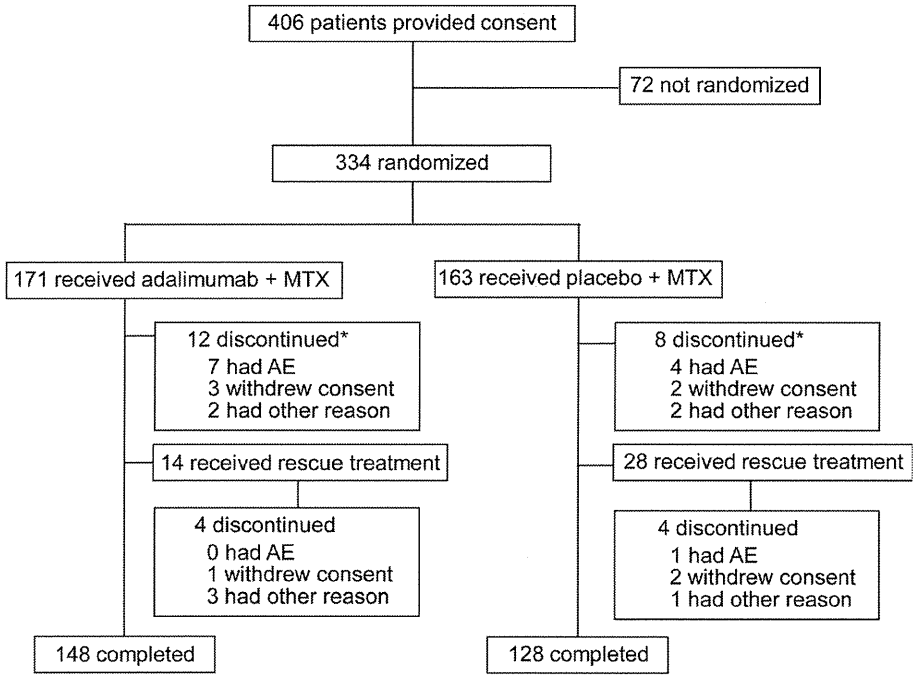


Figure 1 Patient disposition through week 26. *Three adalimumab+MTX patients and one MTX alone patient discontinued from the study by week 26; however, they were included in the efficacy analyses at week 26. AE, adverse event; MTX, methotrexate.

univariate logistic regression analysis was performed, applying 24 baseline demographics and disease characteristics. Significant ($p<0.1$) variables in univariate were included in multivariate models. Last, multivariate models were selected based on model fit statistics (Akaike information criterion and $r^2$) and clinical significance. Adjusted OR and 95% CIs for selected baseline variables were calculated.

## RESULTS

Overall, 334 patients were randomised to treatment and received adalimumab+MTX (n=171) or MTX alone (n=163), and 148 (86.5%) and 128 (78.5%) patients completed the double-blind portion of the study, respectively (figure 1). Demographics and baseline characteristics were well matched between treatment groups (table 1). The mean RA disease duration was 0.3 years, and the majority of patients had ≥1 erosion at baseline and high disease activity. The mean MTX dose during the 26-week study was 6.2±0.8 mg/week in the adalimumab+MTX group and 6.6±0.6 mg/week in the MTX alone group ($p<0.001$). After 26 weeks of treatment, 34.5% (59/171) of adalimumab+MTX patients were receiving MTX 8 mg/week versus 65.0% (106/163) of MTX alone patients ($p<0.001$).

### Radiographic progression

Treatment with adalimumab+MTX significantly inhibited radiographic progression (figure 2A) at week 26 versus MTX alone (mean change±SD, 1.5±6.1 vs 2.4±3.2, respectively; $p<0.001$). Results were confirmed by an LE analysis (figure 2A). Changes in radiographic progression during 26 weeks of treatment were also assessed by a cumulative probability plot of ΔmTSS (figure 2B). Fewer adalimumab+MTX patients exhibited radiographic progression (ΔmTSS>0.5), with 62.0% (106/171) of patients showing no radiographic progression versus 35.4% (57/161) of MTX alone patients ($p<0.001$). Furthermore, only 14.0% (24/171) of adalimumab+MTX patients exhibited clinically relevant radiographic progression (ΔmTSS>3) versus 37.3% (60/161) of MTX alone patients ($p<0.001$). In addition, a significantly higher percentage of adalimumab+MTX patients did not experience worsening (≤0.5) in erosion score (73.7% (126/171)) versus MTX alone patients (42.2% (68/161); $p<0.001$). In patients who lacked baseline erosive damage, the continued absence of erosions was reported in more adalimumab+MTX patients versus MTX alone patients (9/9 vs 2/6 patients, respectively; $p=0.01$).

### Clinical response

A significantly higher percentage of adalimumab+MTX patients achieved ACR responses versus MTX alone patients at each assessment (figure 3A–C). Significant differences between treatment groups, observed as early as week 2, were maintained through week 26. At week 26, a significantly larger percentage of adalimumab+MTX patients versus MTX alone patients achieved ACR20, ACR50 and ACR70 (figure 3A–C) and ACR90 (12.9% vs 5.5%; $p=0.02$) responses. Significant differences in favour of adalimumab+MTX were also observed from week 2 to 26 for DAS28-ESR, DAS28-CRP, SDAI and CDAI (see online supplementary figure 1A–D). A larger percentage of adalimumab+MTX patients than MTX alone patients demonstrated good or moderate European League Against Rheumatism responses (figure 3D) and were in states of low disease activity or remission after 26 weeks of treatment (figure 3E). Furthermore, a significantly larger percentage of adalimumab+MTX patients versus MTX alone patients satisfied Boolean remission criteria (19.3% vs 8.6%, $p=0.007$). Adalimumab+MTX achieved a 1.8- to 2.2-fold increase in the percentage of patients achieving clinical remission, across all definitions of clinical remission evaluated, versus MTX alone.

Table 1 Demographics and baseline characteristics

| Parameter* | Adalimumab+MTX (n=171) | MTX (n=163) |
|---|---|---|
| Age±SD (year) | 54.0±13.1 | 54.0±13.2 |
| Females (n (%)) | 144 (84.2) | 128 (78.5) |
| RA duration±SD (year) | 0.3±0.4 | 0.3±0.4 |
| Weight±SD (kg) | 54.4±9.7 | 56.1±12.3 |
| Previous DMARD use (n (%)) | 74 (43.3) | 87 (53.4) |
| 1 DMARD | 57 (33.3) | 69 (42.3) |
| 2 DMARDs | 17 (9.9) | 18 (11.0) |
| Corticosteroid use at baseline (n (%)) | 58 (33.9) | 49 (30.1) |
| RF positive (n (%)) | 146 (85.4) | 136 (83.4) |
| Mean titre±SD (IU/ml) | 154.5±202.3 | 163.7±362.8 |
| Anti-CCP positive (n (%)) | 145 (84.8) | 136 (83.4) |
| Mean titre±SD (U/ml) | 386.2±694.2 | 241.3±367.2 |
| ESR (mm/h) | 59.9±30.1 | 61.8±29.0 |
| CRP (mg/dl) | 2.9±3.0 | 3.1±3.3 |
| Swollen joint count (n±SD) | | |
| 0–28 | 11.5±4.7 | 11.8±5.3 |
| 0–66 | 16.5±6.2 | 17.3±7.7 |
| Tender joint count (n±SD) | | |
| 0–28 | 13.2±5.8 | 13.2±6.1 |
| 0–68 | 20.7±9.4 | 21.1±10.2 |
| mTSS | 13.6±22.3 | 13.6±17.4 |
| Erosion score | 7.5±11.6 | 7.3±9.2 |
| Joint space narrowing score | 6.2±11.4 | 6.2±9.4 |
| DAS28-ESR | 6.6±0.9 | 6.6±1.0 |
| DAS28-CRP | 5.8±1.0 | 5.9±1.0 |
| HAQ-DI score | 1.1±0.7 | 1.3±0.8 |
| SDAI score | 40.7±12.0 | 41.4±13.8 |
| CDAI score | 37.8±10.9 | 38.3±12.4 |
| Physician's global assessment of disease activity±SD (mm) | 65.8±18.4 | 66.2±18.8 |
| Patient's global assessment of disease activity±SD (mm) | 64.1±24.8 | 66.4±23.7 |

*Data are mean±SD unless otherwise indicated.
CCP, cyclic citrullinated peptide; CDAI, clinical disease activity index; CRP, C reactive protein; DAS28-CRP, disease activity score using a 28-joint count and CRP level; DAS28-ESR, disease activity score using a 28-joint count and ESR; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire disability index; mTSS, modified total Sharp score; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, simplified disease activity index.

A significantly larger decrease from baseline in mean HAQ-DI score, indicative of an improvement in physical function, was observed for adalimumab+MTX patients versus MTX alone patients at week 26 (−0.6±0.6 vs −0.4±0.6; $p<0.001$). Although the significant difference between the two groups was small (0.2 units), the percentage of patients achieving normal functionality (HAQ-DI score<0.5) after 26 weeks of treatment was also significantly higher with adalimumab+MTX (figure 3F).

### Factors associated with the absence of radiographic progression or with clinical remission

Disease activity or function baseline variables generally were associated with the absence of radiographic progression (ΔmTSS≤0.5) and with clinical remission (DAS28-ESR<2.6) in both treatment groups (see online supplementary text and online supplementary table 1).