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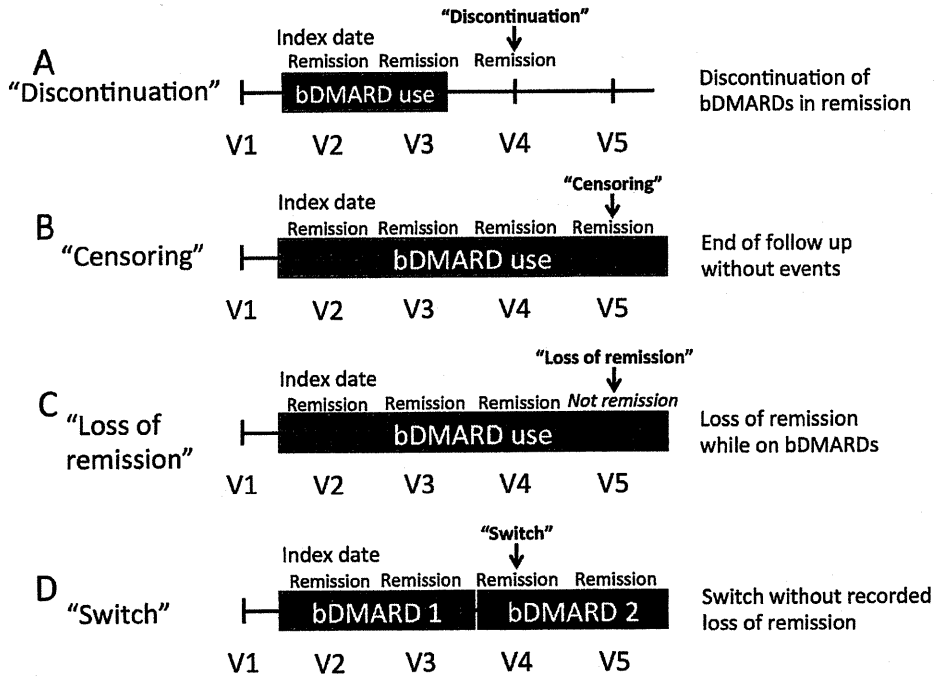
APPENDIX 1. The 4 potential endpoints examined in the study are "discontinuation" (event of interest), "censoring," "loss of remission," or "switch." "Index date" is the start of followup defined as the first of successive visits in remission while receiving bDMARD. "V1–5" denotes the study visits. The shaded boxes indicate visits while receiving bDMARD. "Remission/Not remission" indicates the disease activity at the corresponding visit. "bDMARD 1/bDMARD 2" indicates change in bDMARD in use. (A) If the patient discontinued bDMARD while remaining in remission, it was considered "discontinuation." It is the event of interest. (B) If the patient reached the end of followup without experiencing any of the endpoints, it was considered "censoring." (C) If the patient experienced loss of remission defined by the CDAI, it was considered "loss of remission" and the followup was terminated. (D) If the treatment was changed to a different bDMARD without reported loss of remission, it was considered "switch" and the followup was terminated. "Loss of remission" and "switch" are competing risk events that prevent the event of interest from occurring. bDMARD: biological disease-modifying antirheumatic drugs; CDAI: Clinical Disease Activity Index.



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Concomitant Methotrexate Protects Against Total Knee Arthroplasty in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors

Shuji Asai, Nobunori Takahashi, Koji Funahashi, Yutaka Yoshioka, Toki Takemoto, Kenya Terabe, Nobuyuki Asai, Naoki Ishiguro and Toshihisa Kojima

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ABSTRACT. ***Objective.*** To determine the effects of concomitant methotrexate (MTX) on the incidence of total knee arthroplasty (TKA) resulting from the progression of joint destruction in patients with rheumatoid arthritis (RA) during longterm treatment with tumor necrosis factor (TNF) inhibitors.

Methods. A total of 155 patients with RA (310 knee joints) received TNF inhibitors at our institute between May 1, 2001, and May 31, 2008. A total of 111 symptomatic (tender and/or swollen) knee joints in 68 patients were retrospectively studied over the course of a minimum of 5 years of followup. The median (interquartile range) followup period was 8.1 (7.0–9.3) years. All data were analyzed using the knee joint as the statistical unit of analysis. TKA during treatment with TNF inhibitors was used as the outcome variable in predictive analyses. The cumulative incidence of TKA was compared by concomitant or no MTX use (MTX±).

Results. There were 79 subjects (71%) who received concomitant MTX. According to Kaplan-Meier estimates, the cumulative incidence of TKA for the MTX+ group was significantly lower than that for the MTX– group (24% vs 45% at 5 yrs, respectively, p = 0.035). Multivariate analysis using the Cox proportional hazards model revealed that concomitant MTX (HR 0.44, 95% CI 0.22–0.89), Larsen grade (HR 2.93, 95% CI 1.94–4.41), and older age at baseline (HR 1.04, 95% CI 1.01–1.08) were independent predictors of TKA.

Conclusion. Concomitant MTX reduces the incidence of TKA by 56% in patients with RA during longterm treatment with TNF inhibitors. (First Release October 1 2015; J Rheumatol 2015;4:2255–60; doi:10.3899/jrheum.150410)

Key Indexing Terms:

RHEUMATOID ARTHRITIS TUMOR NECROSIS FACTOR INHIBITOR METHOTREXATE
KNEE JOINT LONGTERM EFFECT TOTAL KNEE ARTHROPLASTY

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with irreversible joint destruction and functional disability; preventing these is the goal of RA therapy[1].

From the Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan.

S. Asai, MD, PhD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine; N. Takahashi, MD, PhD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine; K. Funahashi, MD, PhD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine; Y. Yoshioka, MD, PhD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine; T. Takemoto, MD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine; K. Terabe, MD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine; N. Asai, MD, PhD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine; N. Ishiguro, MD, PhD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine; T. Kojima, MD, PhD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine.

Address correspondence to Dr. S. Asai, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan. E-mail: asai@med.nagoya-u.ac.jp

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Methotrexate (MTX) is an important anchor drug for RA therapy and should be given as soon as a diagnosis is made[2]. Recommendations from the American College of Rheumatology (ACR)[3] and European League Against Rheumatism (EULAR)[4] suggest that treatments with biological disease-modifying antirheumatic drugs (bDMARD) may be considered when the response to MTX with or without glucocorticoids is insufficient and prognostically unfavorable factors are present.

Tumor necrosis factor (TNF) is a key cytokine in the pathogenesis of RA[5], and various TNF inhibitors work by halting inflammatory and destructive disease processes[6,7,8,9,10,11]. TNF inhibitors in combination with MTX reduce disease activity, slow radiographic progression, and improve function to a greater extent than monotherapies of each agent[8,9,10]. However, assessment of joint destruction in these studies was restricted to small joints in the hands and feet at followup periods of 1 and 2 years. Damage to large joints, especially weight-bearing joints such as the knee and hip, has a larger effect on functional disability than damage

to small joints in patients with RA[12,13]. Accordingly, the evaluation of large weight-bearing joints is important when assessing the efficacy of drug therapy for RA, as is the evaluation of small joints. It is also important to evaluate the longterm inhibitory effect of drug therapy on joint damage. Given that total joint arthroplasty is a common procedure for treating damaged large joints, it can serve as a surrogate for the longterm outcome of large joint destruction in patients with RA[14,15,16].

Our study aimed to determine the effects of concomitant MTX on the incidence of total knee arthroplasty (TKA) resulting from the progression of joint destruction in patients with RA during longterm treatment with TNF inhibitors. As residual symptoms including tenderness and swelling have been shown to lead to the destruction of knee joints[17] and small joints[18], we focused on symptomatic (tender and/or swollen) knee joints.

MATERIALS AND METHODS

Subjects. A total of 155 patients with RA (310 knees) received TNF inhibitors at our institute between May 1, 2001, and May 31, 2008. All patients met the 1987 ACR classification criteria[19]. TNF inhibitors were administered according to the drug label and the Japan College of Rheumatology guidelines for treatment. Knee joints that met the following criteria were retrospectively studied: (1) symptomatic (tender and/or swollen) knee joints at the initiation of TNF inhibitors (baseline), (2) radiographic data of knee joints available at baseline, and (3) clinical followup data available for a minimum of 5 years. Knee joints that had already received TKA prior to the initiation of TNF inhibitors were excluded from our study. A flow chart demonstrating the study design is shown in Figure 1. Of 138 symptomatic knee joints, 27 were excluded because of missing baseline radiographic data (n = 8) or loss to followup (n = 19). Thus, a final total of 111 knee joints in 68 patients were analyzed in our study. The median [interquartile range (IQR)] followup period was 8.1 (7.0–9.3) years. Notably, there was no significant difference in most baseline characteristics except for age between analyzed and excluded subjects [median (IQR) 54 (39–62) vs 64 (48–72) yrs, p = 0.007]. Patient anonymity was maintained during data collection, and the security of personal information was strictly controlled. The Ethics Committee of the Nagoya University Graduate School of Medicine approved this study.

Data collection. Demographic and clinical data were recorded at baseline, and included age, sex, body mass index, disease duration, 28-joint Disease Activity Score with C-reactive protein (DAS28-CRP)[20], Larsen grade, the first TNF inhibitor, and concomitant treatment with MTX and/or glucocorticoids. Data regarding the incidence of TKA were retrospectively collected from clinical records. Surgery performed after diagnosis of RA was defined as surgery consequent to RA. Revision surgeries and surgeries attributable to fractures were excluded.

Radiographic assessment. Radiographic assessment of knee joints was performed at baseline. Damage to knee joints was evaluated by 2 observers according to the Larsen method using standard reference films[21]. The Larsen method is most commonly used to evaluate large joints, including the knee, and has reasonable sensitivity and satisfactory intraobserver and interobserver reliability[22]. In cases of disagreement, a consensus was reached by the observers. A grade of I is given when 1 or more of the following lesions are present: soft-tissue swelling, periarticular osteoporosis, and/or slight joint space narrowing. Larsen grades of II–V are given in the event of erosive disease; higher grades indicate more damage. The presence of a huge deformity is assigned the maximum grade of V.

Statistical analysis. To analyze knee joints individually, all data were analyzed using the knee joint as the statistical unit of analysis. Continuous variables are expressed as median and IQR, while categorical variables are expressed as numbers and percentages. Baseline data were compared by concomitant or no MTX use (MTX+ and MTX– groups, respectively) with the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. In predictive analyses, TKA during treatment with TNF inhibitors was used as the outcome variable, and subjects were censored at the time of discontinuation of TNF inhibitors or August 31, 2014, whichever came first. The cumulative incidence of TKA was estimated using Kaplan-Meier curves and compared with the log-rank test. The effect of baseline characteristics on the incidence of TKA was assessed with univariate and stepwise forward multivariate Cox proportional hazards models. The

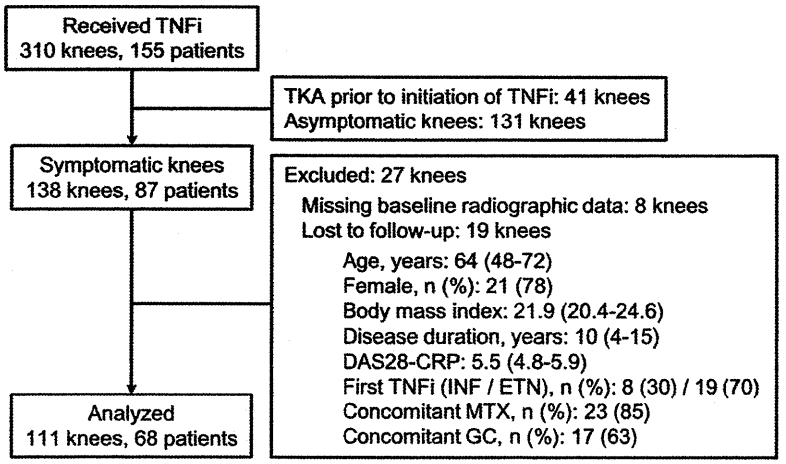

Figure 1. Flowchart depicting the study design. Baseline characteristics of the 27 excluded subjects are presented as median values (interquartile range) or number of subjects (percentage). TNFi: tumor necrosis factor inhibitor; TKA: total knee arthroplasty; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; INF: infliximab; ETN: etanercept; MTX: methotrexate; GC: glucocorticoid.

univariate analyses included the following variables: age, sex, body mass index, disease duration, DAS28-CRP, Larsen grade, the first TNF inhibitor, concomitant MTX, and concomitant glucocorticoids. Variables found to be significant ($p < 0.05$) in univariate analyses were included in the multivariate model. Statistical analyses were performed with SPSS version 20.0.0 software (IBM Corp). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics. Baseline characteristics of all subjects included in our study are shown in Table 1. Agents used as the first TNF inhibitor were infliximab (IFX) and etanercept (ETN) because only these 2 bDMARD were available for use to treat RA in Japan until May 2008. Seventy-nine subjects (71%) received concomitant MTX at a median (IQR) dose of 8 (6–10) mg/week. Based on the Larsen grade of knee joints, 5 joints were categorized as grade 0, 24 as grade I, 26 as grade II, 31 as grade III, 25 as grade IV, and 0 as grade V.

Relative to the MTX– group (n = 32), the MTX+ group (n = 79) was more likely to have a higher rate of IFX as the first TNF inhibitor (59% vs 0%, $p < 0.001$) and a higher concomitant glucocorticoid use (68% vs 41%, $p = 0.007$). There was no significant difference in the other characteristics among groups.

Retention of TNF inhibitor therapy. Of all subjects, 80 (72%) continued treatment with TNF inhibitors over 5 years, with 59 of these continuing the first TNF inhibitor and 21 switching to another TNF inhibitor (data not shown). Of the 31 patients who discontinued TNF inhibitors within 5 years, 18 switched to non-TNF biologics.

Cumulative incidence of TKA. A total of 33 knees underwent TKA during treatment with TNF inhibitors. According to Kaplan-Meier estimates, the overall cumulative incidence of TKA was about 30% at 5 years after initiation of the TNF inhibitor (Figure 2A). We next estimated the incidence of TKA stratified by the following baseline categorical variables: sex, Larsen grade, the first TNF inhibitor, and concomitant treatment with MTX and glucocorticoids. Eighteen of the 79 knees (23%) in the MTX+ group underwent TKA during treatment with TNF inhibitors, while 15 of 32 knees (47%) did so in the MTX– group. According to Kaplan-Meier estimates, the cumulative incidence of TKA for the MTX+ group was significantly lower than that for the MTX– group (24% vs 45% at 5 yrs, respectively, $p = 0.035$; Figure 2B). The cumulative incidence of TKA was significantly higher in knee joints with more severe damage at baseline ($p < 0.001$; Figure 2C). There was no significant difference in the cumulative incidence of TKA stratified by sex, the first TNF inhibitor, or concomitant glucocorticoids.

Effect of baseline characteristics on the incidence of TKA. HR for the incidence of TKA were calculated using Cox proportional hazards models (Table 2). Univariate analysis revealed that older age at baseline (HR 1.04 per 1 yr, 95% CI 1.01–1.07), Larsen grade (HR 2.88 per 1 grade, 95% CI 1.90–4.38), and concomitant MTX (HR 0.49, 95% CI 0.24–0.96) predicted TKA. None of the other variables predicted TKA. We next performed multivariate analysis with age, Larsen grade, and concomitant MTX set as variables. Concomitant MTX predicted TKA (HR 0.44, 95% CI

Table 1. Baseline characteristics by concomitant or no use of MTX with TNFi. Data are median (interquartile range) or n (%) unless otherwise specified.

Characteristics	Total, n = 111	MTX+, n = 79	MTX–, n = 32	p
Age, yrs	54 (39–62)	54 (35–62)	55 (39–62)	0.966
Female	95 (86)	67 (85)	28 (88)	0.715
BMI	21.3 (19.0–24.0)	21.3 (19.0–24.0)	20.6 (18.9–24.1)	0.921
Disease duration, yrs	8 (3–12)	8 (3–13)	7 (4–12)	0.770
DAS28-CRP	5.6 (4.9–6.4)	5.5 (4.8–6.4)	6.3 (5.2–6.7)	0.210
Larsen grade				0.458
Grade 0	5 (4)	5 (6)	0 (0)	
Grade I	24 (22)	18 (23)	6 (19)	
Grade II	26 (23)	16 (20)	10 (31)	
Grade III	31 (28)	23 (29)	8 (25)	
Grade IV	25 (23)	17 (22)	8 (25)	
Grade V	0 (0)	0 (0)	0 (0)	
First TNFi				< 0.001
IFX	47 (42)	47 (59)	0 (0)	
ETN	64 (58)	32 (41)	32 (100)	
Concomitant MTX	79 (71)	—	—	—
MTX dose, mg/week*	—	8 (6–10)	—	—
Concomitant GC	67 (60)	54 (68)	13 (41)	0.007
GC dose, mg/day*†	5 (5–5)	5 (5–7.5)	5 (5–5)	0.413

*Median among subjects receiving the drug. †Prednisolone equivalent (mg/day). MTX: methotrexate; TNFi: tumor necrosis factor inhibitor; BMI: body mass index; DAS28: Disease Activity Score at 28 joints; CRP: C-reactive protein; IFX: infliximab; ETN: etanercept; GC: glucocorticoid.

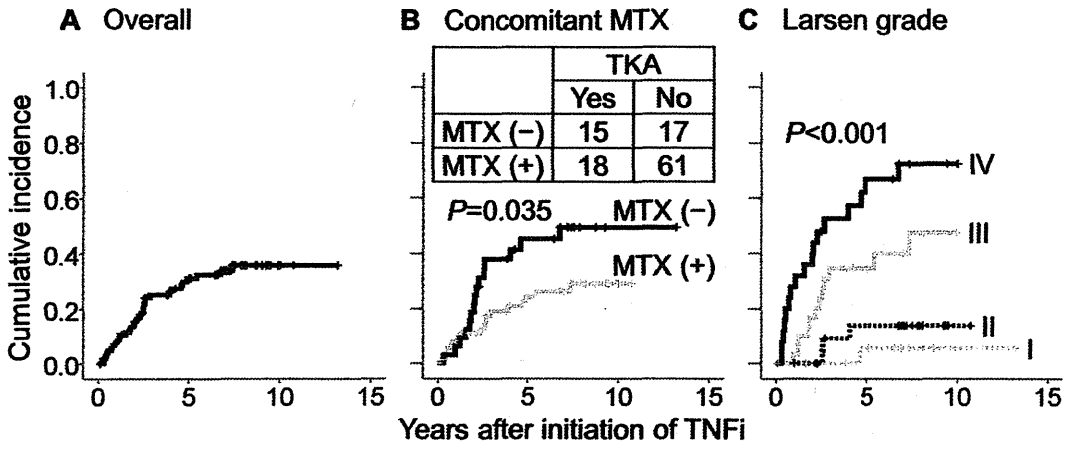

Figure 2. Kaplan-Meier estimates of overall cumulative incidence of TKA (A), and cumulative incidence stratified by concomitant MTX (B) and Larsen grade (C). TNFi: tumor necrosis factor inhibitor; MTX: methotrexate; TKA: total knee arthroplasty.

Table 2. Effect of baseline variables on the incidence of TKA. Data are median (interquartile range) or n unless otherwise specified.

Variables	TKA		HR (95% CI)	
	Yes, n = 33	No, n = 78	Univariate	Multivariate
Age, yrs	59 (52–63)	52 (34–59)	1.04 (1.01–1.07)*	1.04 (1.01–1.08)*
Sex				
Male, reference	5	11	1	—
Female	28	67	1.16 (0.45–3.02)	—
BMI	21.3 (19.0–24.0)	21.3 (19.0–24.0)	0.99 (0.89–1.10)*	
Disease duration, yrs	5 (4–16)	8 (2–12)	1.01 (0.97–1.06)*	—
DAS28-CRP	6.3 (4.9–6.7)	5.5 (4.9–6.4)	1.42 (0.96–2.12)*	—
Larsen grade			2.88 (1.90–4.38)*	2.93 (1.94–4.41)*
Grade 0	0	5		
Grade I	1	23		
Grade II	3	23		
Grade III	12	19		
Grade IV	17	8		
Grade V	0	0		
First TNFi				
IFX, reference	11	36	1	—
ETN	22	42	1.31 (0.63–2.70)	—
Concomitant MTX				
No, reference	15	17	1	1
Yes	18	61	0.49 (0.24–0.96)	0.44 (0.22–0.89)
Concomitant GC				
No, reference	11	33	1	—
Yes	22	45	1.44 (0.70–3.00)	—

*HR for 1-unit increase in each item. TKA: total knee arthroplasty; BMI: body mass index; DAS28: Disease Activity Score at 28 joints; CRP: C-reactive protein; TNFi: tumor necrosis factor inhibitor; IFX: infliximab; ETN: etanercept; MTX: methotrexate; GC: glucocorticoid.

0.22–0.89) independently of age and Larsen grade at baseline.

DISCUSSION

Our study clearly demonstrated the effects of concomitant MTX on the incidence of TKA as a surrogate for the longterm outcome of joint destruction in patients with RA treated with TNF inhibitors. We analyzed knee joints individually with a minimum of 5 years of followup. Previous studies reported that joint damage existing at baseline was a risk factor for the

progression of knee joint destruction in patients with RA treated with TNF inhibitors[17,23]. Interestingly, our multivariate analysis revealed that concomitant MTX predicted the incidence of TKA independently of joint damage at baseline. Various TNF inhibitors in combination with MTX have been shown to be significantly superior to monotherapies of each agent in inhibiting radiographic progression in the TEMPO[8] and PREMIER[9] studies. However, the assessment of radiographic progression in these studies was restricted to small joints, as measured by the total Sharp score. To our knowledge, our study is the first to demonstrate that concomitant MTX may inhibit the destruction of large weight-bearing joints in patients with RA treated with TNF inhibitors, and strongly supports the EULAR recommendations to commence MTX with all bDMARD[4].

Notably, the dose of MTX [median (IQR), 8 (6–10) mg/week] in those who used it in our present study was lower than the doses used in the TEMPO[8] and PREMIER[9] studies (mean 16–17 mg/week), even after considering that the average body weight of patients in Japan is 20–30% less than that in the United States and Europe. This is because the dose of MTX approved by the Japanese Ministry of Health, Labor, and Welfare had an upper limit of 8 mg/week until January 2011. This was subsequently increased to 16 mg/week in February 2011 for patients with RA. A systematic literature review of MTX monotherapy recommended starting oral MTX at 10–15 mg/week and escalating the dose up to 20–30 mg/week, depending on clinical response and tolerability[24]. However, little is known about the minimally effective dose of MTX when used in combination with a TNF inhibitor in patients with RA. Recently, the CONCERTO trial demonstrated that MTX at 10 mg/week can be used in combination with TNF inhibitors[25]. The unique situation in Japan has provided interesting data showing that concomitant MTX 7–8 mg/week works in an additive manner with TNF inhibitors[26,27,28]. These studies support our finding that concomitant use of even a low dose of MTX may help reduce the incidence of TKA in patients treated with TNF inhibitors.

According to 1 study, the median duration of disease at the time of total joint arthroplasty was 9.1 years in patients with RA[14]. This suggests that evaluation of the incidence of total joint arthroplasty requires longterm followup. In our present study, 111 subjects (80.4%) were followed up for more than 5 years, at a median followup period of 8.1 years. This is the main strength of our study because the duration of followup is likely to be sufficiently long to assess large joint destruction, given the median disease duration at baseline of 8 years.

Not all TKA are attributable to RA alone, given the difficulty of distinguishing between degenerative and inflammatory processes leading to joint surgery. Our study, as well as previous studies[15,29], identified age as a predictor of TKA. Degenerative changes, such as those seen in osteoarthritis, may affect the incidence of TKA, especially in older patients.

Our study has some limitations worth noting. First, this is a retrospective study of patients with RA treated with TNF inhibitors. We were able to evaluate the effectiveness of treatment in real clinical settings, but potential biases are certainly present, including selection bias for treatment. Decisions regarding treatment, including concomitant MTX use and surgical intervention, were based on physician discretion. Indeed, significant differences between the MTX+ and MTX– groups were found with regard to the first TNF inhibitor and concomitant glucocorticoid use, although these did not significantly influence the incidence of TKA. A well-designed randomized controlled trial will be required to estimate the efficacy of treatment with more certainty. Second, as with other studies[30,31,32], we analyzed all data using the knee joint as the statistical unit of analysis. A potential bias exists from including bilateral knee joints. Finally, the sample size was too small for robust results, and the significance of some of the findings may change with a larger dataset.

Concomitant MTX effectively reduces the incidence of TKA by 56% in patients with RA during longterm treatment with TNF inhibitors. Our findings suggest that TNF inhibitors should be used preferentially in combination with MTX to inhibit the progression of large joint destruction as well as small joint destruction, and also strongly support the EULAR recommendations. Moreover, our study suggests that low-dose MTX may have an additive effect on TNF inhibitor treatment of RA.

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ORIGINAL ARTICLE

Effects of Concomitant Methotrexate on Large Joint Replacement in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Inhibitors: A Multicenter Retrospective Cohort Study in Japan

SHUJI ASAI,[1] TOSHIHISA KOJIMA,[1] TAKESHI OGUCHI,[2] ATSUSHI KANEKO,[3] YUJI HIRANO,[4] YUICHIRO YABE,[5] YASUHIDE KANAYAMA,[6] NOBUNORI TAKAHASHI,[1] KOJI FUNAHASHI,[1] MASAHIRO HANABAYASHI,[7] SHINYA HIRABARA,[4] YUTAKA YOSHIOKA,[1] TOKI TAKEMOTO,[1] KENYA TERABE,[1] NOBUYUKI ASAI,[1] AND NAOKI ISHIGURO[1]

Objective. To determine the effects of concomitant methotrexate (MTX) on the incidence of large joint replacement resulting from the progression of large joint destruction in patients with rheumatoid arthritis (RA) treated with tumor necrosis factor (TNF) inhibitors.

Methods. A retrospective cohort study was performed using a multicenter registry. In total, 803 patients with RA who received etanercept or adalimumab were included. The first large joint replacement during treatment with etanercept or adalimumab was used as the outcome variable in predictive analyses. The cumulative incidence of large joint replacement was estimated using Kaplan-Meier curves, and the impact of concomitant MTX on the incidence of large joint replacement was assessed with Cox proportional hazards models. Propensity score matching was used to reduce selection bias.

Results. Of all patients, 601 (75%) received concomitant MTX at a median dosage of 8 mg/week (interquartile range 6–8). A total of 49 patients (62 joints) underwent large joint replacement during treatment with etanercept or adalimumab. The incidence of large joint replacement for patients with concomitant MTX was significantly lower than that for patients without MTX ($P < 0.001$). Multivariate analysis revealed that concomitant MTX independently predicted large joint replacement (hazard ratio 0.36, 95% confidence interval 0.20–0.65). Additionally, propensity score–matched analysis demonstrated that patients with concomitant MTX had a significantly lower incidence of large joint replacement than those without concomitant MTX ($P = 0.032$).

Conclusion. Concomitant MTX reduces the incidence of large joint replacement in patients with RA treated with TNF inhibitors.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with irreversible joint destruction and functional disability; preventing these is the goal of RA treatment (1). Methotrexate (MTX) is an important anchor drug for RA treatment and should be given as soon as the diagnosis is made (2). The recommendations of the American College of Rheumatology (ACR) (3) and European

[1]Shuji Asai, MD, PhD, Toshihisa Kojima, MD, PhD, Nobunori Takahashi, MD, PhD, Koji Funahashi, MD, PhD, Yutaka Yoshioka, MD, PhD, Toki Takemoto, MD, Kenya Terabe, MD, Nobuyuki Asai, MD, Naoki Ishiguro, MD, PhD: Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]Takeshi Oguchi, MD, PhD: Anjo Kosei Hospital, Anjo, Japan; [3]Atsushi Kaneko, MD: Nagoya Medical Center, Nagoya, Japan; [4]Yuji Hirano, MD, PhD, Shinya Hirabara, MD, PhD: Toyohashi Municipal Hospital, Toyohashi, Japan; [5]Yuichiro Yabe, MD, PhD: Tokyo Shinjuku Medical Center, Tokyo, Japan; [6]Yasuhide Kanayama, MD, PhD: Toyota Kosei Hospital, Toyota, Japan; [7]Masahiro Hanabayashi, MD: Ichinomiya Municipal Hospital, Ichinomiya, Japan.

Dr. S. Asai has received speaking fees (less than $10,000) from Eisai. Dr. Kojima has received speaking fees (less than $10,000 each) from Mitsubishi Tanabe, Takeda, Eisai, Abbott, Bristol-Myers Squibb, and Pfizer, and (more than $10,000) from Chugai. Dr. Kaneko has received speaking fees (less than $10,000 each) from Mitsubishi Tanabe, Takeda, Eisai, Abbott, Bristol-Myers Squibb, and Pfizer, and (more than $10,000) from Chugai. Dr. Hirano has received speaking fees (less than $10,000 each) from Mitsubishi Tanabe, Takeda, Eisai, Abbott, Bristol-Myers Squibb, and Pfizer, and (more than $10,000) from Chugai. Dr. Ishiguro has received speaking fees (less than $10,000 each) from Mitsubishi Tanabe, Takeda, Eisai, Chugai, Abbott, Bristol-Myers Squibb, and Pfizer.

Significance & Innovations

- Concomitant methotrexate (MTX) effectively reduces the incidence of large joint replacement in patients with rheumatoid arthritis (RA) treated with tumor necrosis factor (TNF) inhibitors.
- Our findings not only suggest that TNF inhibitors should be used preferentially in combination with MTX to inhibit the progression of both large and small joint destruction, but also strongly support recent European League Against Rheumatism recommendations.
- Low-dose MTX may have an additive effect on TNF inhibitor treatment for RA.

League Against Rheumatism (EULAR) (4) suggest that treatments with biologic disease-modifying antirheumatic drugs (DMARDs) should be considered when the response to MTX with or without glucocorticoids is insufficient and prognostically unfavorable factors are present.

Tumor necrosis factor (TNF) is a key cytokine in the pathogenesis of RA (5), and various TNF inhibitors work by halting inflammatory and destructive disease processes (6–11). Etanercept and adalimumab in combination with MTX have been shown to reduce disease activity, slow radiographic progression, and improve function to a greater extent than monotherapies of each agent (8,9). However, assessment of joint destruction in these studies was restricted to small joints in the hands and feet. Functional disability is impacted by damage to large joints, such as the shoulder, elbow, hip, knee, and ankle, as well as damage to small joints in patients with RA (12,13). Accordingly, evaluation of large and small joints is important when assessing the efficacy of TNF inhibitors. Given that total joint replacement is a common procedure for treating damaged large joints, it can serve as a surrogate for severe large joint destruction in patients with RA (14–16).

This study aimed to determine the effects of concomitant MTX on the incidence of large joint replacement resulting from the progression of large joint destruction in patients with RA treated with TNF inhibitors.

PATIENTS AND METHODS

Patients. A multicenter retrospective cohort study was performed using the Tsurumai Biologics Communication Registry (TBCR), an RA research consortium that consists of Nagoya University Hospital and 12 affiliated institutions (17). TBCR was initiated in October 2008 to study the long-term efficacy and safety of treatment with biologic DMARDs in patients with RA. Information on demographic and clinical characteristics is available for patients with RA treated with commercially available biologic DMARDs in Japan at TBCR institutes. Data were collected retrospectively from 2003–2008 and prospectively after 2008. Of the patients registered retrospectively until 2008, those for whom information on baseline characteristics was available were selected for this study. The present study included 803 patients with RA who received etanercept (n = 530) or adalimumab (n = 273) between April 1, 2005, and September 30, 2013. Of the 803 patients, 317 (39%) were entered into the registry retrospectively and 486 (61%) were entered prospectively. All patients met the 1987 ACR classification criteria for RA (18) or the new ACR/EULAR diagnostic criteria (19), and received etanercept or adalimumab infusions according to the drug label and Japan College of Rheumatology guidelines for treatment. Patient anonymity was maintained during data collection, and the security of personal information was strictly controlled. This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine.

Address correspondence to Shuji Asai, MD, PhD, Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan. E-mail: asai@med.nagoya-u.ac.jp.

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Data collection. Demographic and clinical data were recorded at the initiation of treatment with etanercept or adalimumab (baseline), and included age, sex, disease duration, Steinbrocker stage and class, Disease Activity Score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR) (20), history of previous large joint replacement, history of previous treatment with biologic DMARDs, and concomitant treatment with MTX and/or glucocorticoids. Data regarding the incidence of large joint replacement were retrospectively collected from clinical records. Surgery performed after diagnosis of RA was defined as surgery consequent to RA. Revision surgeries and surgeries due to fractures were excluded.

Statistical analysis. Statistical analyses were performed with SPSS software, version 20.0.0 (IBM). *P* values less than 0.05 were considered statistically significant. Continuous variables are shown as the median and interquartile range (IQR), whereas categorical variables are shown as the number and percentage. Baseline data were compared by concomitant or no MTX use with the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables.

In predictive analyses, the first large joint replacement during treatment with etanercept or adalimumab was used as the outcome variable, and patients were censored at the time of discontinuation of etanercept or adalimumab, loss to followup, or September 30, 2013, whichever came first. The cumulative incidence of large joint replacement was estimated using Kaplan-Meier curves and compared with the log rank test. The impact of concomitant MTX on the incidence of large joint replacement was assessed with univariate and stepwise forward multivariate Cox proportional hazards models with the following variables: age, sex, disease duration, Steinbrocker stage, DAS28-ESR, previous large joint replacement, TNF inhibitors, previous use of biologic DMARDs, concomitant MTX, and concomitant glucocorticoids.

The present cohort was not randomized. Propensity score matching was performed given concerns of treatment selection bias. Propensity score matching is widely used to reduce selection bias in observational studies (21). In this study, the probability score was estimated using a multivariate logistic regression model predicting concomitant use of MTX versus no concomitant use of MTX using the following variables: age, sex, disease duration, DAS28-ESR, history of previous large joint replacement, TNF inhibitors, history of previous treatment with biologic DMARDs, and concomitant treatment with glucocorticoids. Greedy propensity score matching was implemented (1:1 matching using a caliper of 0.01). In greedy matching, once a match is created, the subject is removed from any further consideration for matching (22). Kaplan-Meier curves were generated after matching for the incidence of large joint replacement.

RESULTS

Patient characteristics. Baseline characteristics of all patients included in this study are shown in Table 1. Data for Steinbrocker stage and class were available for 718 and 722 patients, respectively, while the other data were available for all patients. Of the 803 patients, 601 (75%) received concomitant MTX at a median dosage of 8 mg/week (IQR 6–8; ≤8 mg/week, 81% and >8 mg/week, 19%). Relative to patients without concomitant MTX, those with concomitant MTX were more likely to be younger (median age 57 years [IQR 44–66 years] versus 64 years [IQR 54–71 years]; $P < 0.001$) and have a shorter disease duration (median 7 years [IQR 2–14 years] versus 10 years [IQR 4–19 years]; $P < 0.001$), a lower DAS28-ESR score (median 5.2 [IQR 4.6–6.0] versus 5.6 [IQR 4.8–6.4]; $P = 0.003$), a higher rate of adalimumab use (36% versus 27%; $P = 0.019$), and a lower rate of concomitant glucocorticoid use (60% versus 70%; $P = 0.011$). The median followup period was 2.9 years (IQR 1.0–4.6 years), and 37 patients (4.6%) were lost to followup during therapy. There were no significant differences between patients with and without concomitant MTX in the followup period (median 2.7 years [IQR 0.9–4.5 years] versus 3.2 [IQR 1.1–5.1]; $P = 0.094$) or the percentage of those lost to followup (4.5% versus 5.0%; $P = 0.788$).

Incidence of large joint replacement. A total of 49 patients (62 joints, including 36 knees, 17 hips, 8 elbows, and 1 ankle) underwent large joint replacement during

Table 1. Baseline characteristics of patients by concomitant or no use of MTX with TNF inhibitors*

	Total (n = 803)	Concomitant MTX (n = 601)	No concomitant MTX (n = 202)	*P*
Age, median (IQR) years	59 (46–67)	57 (44–66)	64 (54–71)	< 0.001
Female sex, no. (%)	664 (83)	496 (83)	168 (83)	0.835
Disease duration, median (IQR) years	7 (3–16)	7 (2–14)	10 (4–19)	< 0.001
Steinbrocker stage, no.				0.012
I	95	80	15	
II	139	108	31	
III	245	190	55	
IV	239	164	75	
Steinbrocker class, no.				0.001
I	171	133	38	
II	316	255	61	
III	218	145	73	
IV	17	11	6	
DAS28-ESR, median (IQR)	5.3 (4.6–6.1)	5.2 (4.6–6.0)	5.6 (4.8–6.4)	0.003
Previous large joint replacement, no. (%)	123 (15)	86 (14)	37 (18)	0.171
TNF inhibitor, no. (%)				0.019
Etanercept	530 (66)	383 (64)	147 (73)	
Adalimumab	273 (34)	218 (36)	55 (27)	
Previous use of biologic DMARDs, no. (%)	179 (22)	140 (23)	39 (19)	0.239
Concomitant MTX, no. (%)	601 (75)	–	–	–
MTX dosage, median (IQR) mg/week†	–	8 (6–8)	–	–
Concomitant GCs, no. (%)	500 (62)	359 (60)	141 (70)	0.011
GC dosage, median (IQR) mg/day‡	5 (3–5)	5 (3–5)	5 (5–5)	< 0.001

* MTX = methotrexate; TNF = tumor necrosis factor; IQR = interquartile range; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; DMARDs = disease-modifying antirheumatic drugs; GCs = glucocorticoids.
† Median among patients receiving the drug.
‡ Prednisolone mg/day or equivalent. Median among patients receiving the drug.

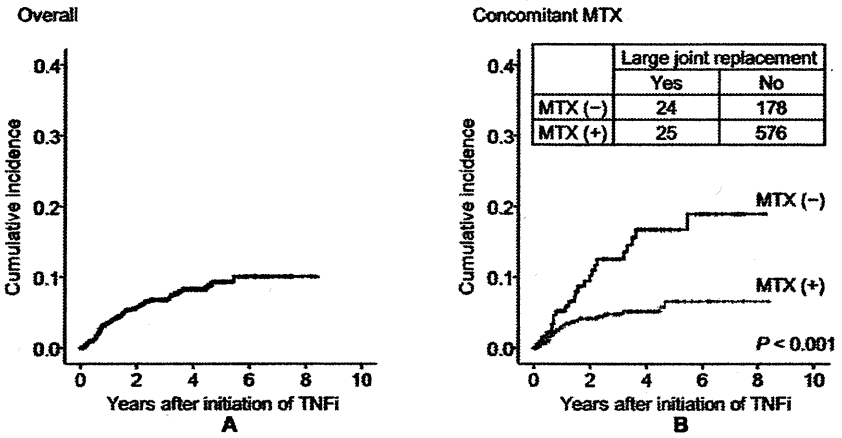

Figure 1. Kaplan-Meier estimates of **A,** overall cumulative incidence of large joint replacement and **B,** cumulative incidence according to concomitant methotrexate (MTX). TNFi = tumor necrosis factor inhibitor.

treatment with etanercept or adalimumab; 36 underwent 1 joint replacement and 13 underwent 2 joint replacements. According to Kaplan-Meier estimates, the overall cumulative incidence of large joint replacement was approximately 10% at 5 years after initiation of etanercept or adalimumab (Figure 1A). The incidence of large joint replacement for patients with concomitant MTX was significantly lower than that for patients without MTX (by log rank test, $P < 0.001$) (Figure 1B). To assess the potential confounding effect of age, patients were divided into 2 groups based on age: <60 years (n = 415) and ≥60 years (n = 388) (Figures 2A and B). The incidence of large joint replacement among patients with concomitant MTX was significantly lower than that for patients without MTX in both groups.

Impact of concomitant MTX on the incidence of large joint replacement. Hazard ratios (HRs) for the incidence of large joint replacement were calculated using Cox proportional hazards models (Table 2). Univariate analysis revealed that concomitant MTX (HR 0.36, 95% confidence interval [95% CI] 0.20–0.63), older age (HR 1.04 per 1 year, 95% CI 1.01–1.06), longer disease duration (HR 1.03 per 1 year, 95% CI 1.01–1.06), Steinbrocker stage (HR 1.73 per 1 stage, 95% CI 1.19–2.51), and previous use of biologic DMARDs (HR 1.94, 95% CI 1.07–3.53) predicted large joint replacement. Since data for Steinbrocker stage were not available for all patients, Steinbrocker stage as a variable was either excluded (model 1, n = 803) or included (model 2, n = 718) in the multivariate analysis. Multivariate analysis revealed that concomitant MTX independently predicted large joint replacement in both model 1 (HR 0.36, 95% CI 0.20–0.65) and model 2 (HR 0.37, 95% CI 0.20–0.69).

Propensity score–matched analysis. A total of 177 matched pairs of patients were identified upon propensity score matching. There was good balance across all base-

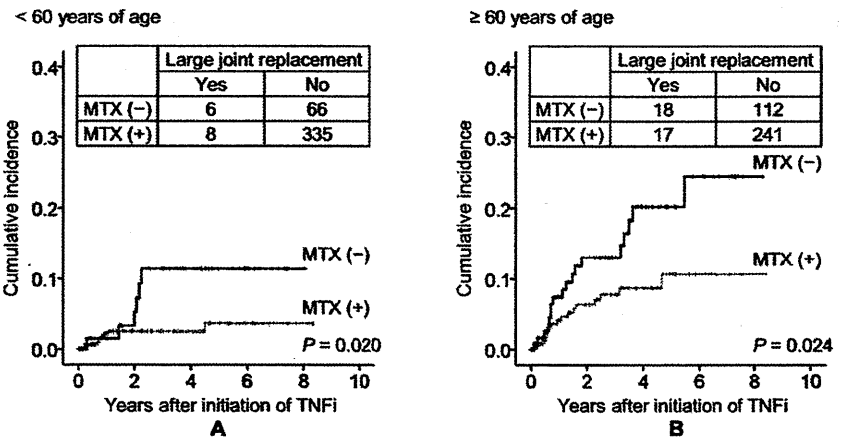

Figure 2. Kaplan-Meier estimates of cumulative incidence of large joint replacement according to concomitant methotrexate in **A,** patients ages <60 years, and **B,** patients ages ≥60 years. MTX = methotrexate; TNFi = tumor necrosis factor inhibitor.

Table 2. Impact of baseline variables on the incidence of large joint replacement*

	Large joint replacement			Multivariate, HR (95% CI)	
	Yes (n = 49)	No (n = 754)	Univariate, HR (95% CI)	Model 1	Model 2
Age, median (IQR) years	64 (56–71)	58 (45–67)	1.04 (1.01–1.06)†	1.03 (1.01–1.06)†	1.03 (1.00–1.05)†
Sex, no.					
Male (ref.)	6	133	1	–	–
Female	43	621	1.45 (0.61–3.41)	–	–
Disease duration, median (IQR) years	13 (8–19)	7 (2–15)	1.03 (1.01–1.06)†	–	–
Steinbrocker stage, no.			1.73 (1.19–2.51)†	–	1.61 (1.11–2.34)†
I	1	94			
II	4	135			
III	16	229			
IV	23	216			
DAS28-ESR, median (IQR)	5.7 (4.9–6.2)	5.3 (4.6–6.1)	1.08 (0.86–1.36)†	–	–
Previous large joint replacement, no.					
No (ref.)	41	639	1	–	–
Yes	8	115	0.96 (0.45–2.05)	–	–
TNF inhibitor, no.					
Etanercept (ref.)	37	493	1	–	–
Adalimumab	12	261	0.90 (0.46–1.72)	–	–
Previous use of biologic DMARDs, no.					
No (ref.)	33	591	1	1	1
Yes	16	163	1.94 (1.07–3.53)	2.32 (1.27–4.25)	2.23 (1.16–4.27)
Concomitant methotrexate, no.					
No (ref.)	24	178	1	1	1
Yes	25	576	0.36 (0.20–0.63)	0.36 (0.20–0.65)	0.37 (0.20–0.69)
Concomitant glucocorticoids, no.					
No (ref.)	24	279	1	1	1
Yes	25	475	0.59 (0.34–1.03)	0.50 (0.28–0.87)	0.53 (0.29–0.96)

* HR = hazard ratio; 95% CI = 95% confidence interval; IQR = interquartile range; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; TNF = tumor necrosis factor; DMARDs = disease-modifying antirheumatic drugs.
† HR for 1-unit increase in each item.

Table 3. Baseline characteristics of patients after propensity score matching*

	Total (n = 354)	Concomitant MTX (n = 177)	No concomitant MTX (n = 177)	*P*
Age, median (IQR) years	62 (52–69)	61 (51–69)	63 (53–69)	0.410
Female sex, no. (%)	298 (84)	153 (86)	145 (82)	0.244
Disease duration, median (IQR) years	9 (4–17)	10 (5–17)	8 (3–16)	0.137
DAS28-ESR, median (IQR)	5.5 (4.8–6.2)	5.5 (4.8–6.2)	5.5 (4.7–6.3)	0.969
Previous large joint replacement, no. (%)	57 (16)	27 (15)	30 (17)	0.664
TNF inhibitor, no. (%)				0.908
Etanercept	245 (69)	122 (69)	123 (69)	
Adalimumab	109 (31)	55 (31)	54 (31)	
Previous use of biologic DMARDs, no. (%)	86 (24)	48 (27)	38 (21)	0.215
Concomitant glucocorticoids, no. (%)	247 (70)	130 (73)	117 (66)	0.132

* MTX = methotrexate; IQR = interquartile range; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; TNF = tumor necrosis factor; DMARDs = disease-modifying antirheumatic drugs.

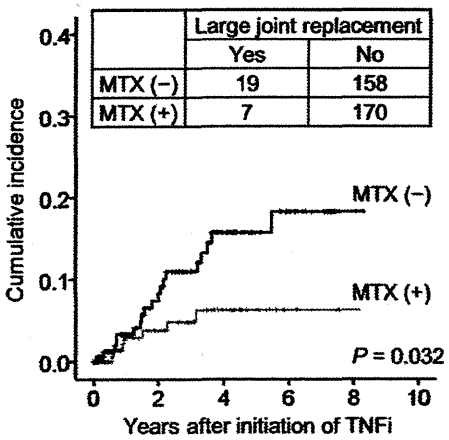

Figure 3. Kaplan-Meier estimates of cumulative incidence of large joint replacement according to concomitant methotrexate (MTX) in a propensity score–matched population. TNFi = tumor necrosis factor inhibitor.

line characteristics (Table 3). Kaplan-Meier curves demonstrated that the incidence of large joint replacement for patients with concomitant MTX was significantly lower than that for patients without MTX ($P = 0.032$) (Figure 3).

DISCUSSION

Total joint replacement is performed when severe large joint destruction causes functional disability. In a sense, total joint replacement represents the failure of medical treatment to control RA adequately, and the incidence of total joint replacement is a measure of disease progression and the ineffectiveness of treatment (14). The incidence of total joint replacement decreases with time, likely due to advances in RA treatment with MTX and biologic DMARDs (23–27). A previous study suggested that in order to inhibit the need for total joint replacement in patients treated with TNF inhibitors, it is important to maintain tight control over RA activity (28).

This study investigated the effects of concomitant MTX on the incidence of large joint replacement in patients with RA treated with TNF inhibitors. Multivariate analysis identified concomitant MTX as an independent predictor of large joint replacement. However, since this was a nonrandomized cohort study, significant differences between patients with and without concomitant MTX were found in the following baseline characteristics: age, disease duration, DAS28-ESR, TNF inhibitors, and concomitant glucocorticoid use. Therefore, in an effort to control for selection bias, we also used propensity score–matched analysis. This analysis revealed that concomitant MTX led to a significantly lower incidence of large joint replacement. Etanercept and adalimumab in combination with MTX have been shown to be significantly superior to monotherapies of each agent in inhibiting radiographic progression in the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) (8) and PREMIER (9) studies. However, the assessment of radiographic progression in these studies was restricted to small joints, as measured by the total Sharp score. Our study is the first to demonstrate that concomitant MTX may inhibit the progression of large joint destruction in patients with RA treated with TNF inhibitors, and strongly supports recent EULAR recommendations to commence MTX with all biologic DMARDs (4).

Noteworthy is the fact that the dosage of MTX (median 8 mg/week [IQR 6–8]) in those who used it in the present study was low compared to the dosages used in the TEMPO and PREMIER studies (mean 16–17 mg/week), even after considering that the average body weight of patients in Japan is 20–30% less than that in the US and Europe. This is because the dosage of MTX approved by the Japanese Ministry of Health, Labour, and Welfare had an upper limit of 8 mg/week until January 2011. This was subsequently increased to 16 mg/week for patients with RA in February 2011. A systematic literature review of MTX monotherapy revealed recommendations to start oral MTX at 10–15 mg/week, with escalation up to 20–30 mg/week depending on clinical response and tolerability (29). However, little is known about the minimally effective dose of MTX when used in combination with a TNF inhibitor in patients with RA. Recently, the CONCERTO trial demonstrated that 10 mg/week of MTX is a possible dosage for use in combination with TNF inhibitors (30). Moreover, the unique situation in Japan has provided interesting data showing that concomitant MTX of 7–8 mg/week works additively with TNF inhibitors (31–33). These studies support our finding that concomitant use of even a low dose of MTX may be useful for reducing the incidence of large joint replacement in patients treated with TNF inhibitors.

Our Kaplan-Meier analysis demonstrated that the incidence of large joint replacement increased rapidly within the first year after initiation of etanercept or adalimumab, both in patients treated with and without concomitant MTX (Figures 1B and 3). A previous study reported that damaged weight-bearing joints of Larsen grades III and IV at baseline showed apparent progression of joint damage after 1 year of TNF inhibitor therapy, even in patients with good clinical response (34). The increased incidence within the first year may be due to joint damage existing before treatment with TNF inhibitors.

Defining "RA-related" surgery is not insignificant, given the difficulty of distinguishing between degenerative and inflammatory processes leading to joint surgery. We adopted the general approach used in other studies (24,35), in which any surgery performed after an RA diagnosis is treated as being related to RA. This study, as well as previous studies (15,24), identified age as a predictor of large joint replacement. Degenerative changes, such as those seen in osteoarthritis, may affect the incidence of large joint replacement, especially in older patients.

This study has some limitations worth noting. First, this is a retrospective cohort study of patients with RA treated with etanercept or adalimumab. We were able to evaluate the effectiveness of treatment in real clinical settings, but potential biases are certainly present, including selection bias for treatment. Decisions regarding treatment, including concomitant MTX use and surgical intervention, were

based on physician discretion. To address this, we used propensity score matching, an advanced epidemiologic method, to reduce selection bias. However, a well-designed randomized controlled trial will be required to estimate the efficacy of treatment with more certainty. Second, the registry does not include radiographic data, which are needed to evaluate joint damage. Additionally, this study was not designed to assess joint destruction directly. Future studies that include radiographic evaluation are warranted. Finally, the sample size was too small for robust results, and the significance of some of the findings may change with a larger data set.

In conclusion, concomitant MTX effectively reduces the incidence of large joint replacement in patients with RA treated with TNF inhibitors. Our findings suggest that TNF inhibitors should be used preferentially in combination with MTX to inhibit the progression of both large and small joint destruction, and also strongly support recent EULAR recommendations. Moreover, this study suggests that low-dose MTX may have an additive effect on TNF inhibitor treatment for RA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. S. Asai had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. S. Asai, Kojima.

Acquisition of data. S. Asai, Kojima, Oguchi, Kaneko, Hirano, Yabe, Kanayama, Takahashi, Funahashi, Hanabayashi, Hirabara, Yoshioka, Takemoto, Terabe, N. Asai, Ishiguro.

Analysis and interpretation of data. S. Asai.

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Concise report

Use of a 12-week observational period for predicting low disease activity at 52 weeks in RA patients treated with abatacept: a retrospective observational study based on data from a Japanese multicentre registry study

Nobunori Takahashi[1], Toshihisa Kojima[1], Atsushi Kaneko[2], Daihei Kida[2], Yuji Hirano[3], Takayoshi Fujibayashi[4], Yuichiro Yabe[5], Hideki Takagi[6], Takeshi Oguchi[7], Hiroyuki Miyake[8], Takefumi Kato[9], Naoki Fukaya[10], Masatoshi Hayashi[11], Seiji Tsuboi[12], Yasuhide Kanayama[13], Koji Funahashi[1], Masahiro Hanabayashi[1], Shinya Hirabara[1], Shuji Asai[1], Yutaka Yoshioka[1] and Naoki Ishiguro[1]

Abstract

Objective. Only a few studies have assessed predictive factors for the long-term efficacy of abatacept. This study aimed to provide clinical evidence of an adequate observational period for predicting low disease activity (LDA) achievement at 52 weeks in RA patients treated with abatacept.

Methods. Participants were all patients registered in a Japanese multicentre registry who were treated with abatacept and had at least 52 weeks of follow-up ($n = 254$).

Results. Areas under the receiver operating characteristic curves for the 28-joint count with CRP (DAS28-CRP) at each time point for LDA achievement at 52 weeks were: 0.686 (cut-off score: 4.6) at baseline, 0.780 (3.8) at 4 weeks, 0.875 (3.3) at 12 weeks, and 0.900 (3.0) at 24 weeks. Although patients with a DAS28-CRP score < 3.0 at 24 weeks had the highest proportion of LDA achievement at 52 weeks (79.3%), the proportion for those with a score < 3.3 at 12 weeks was comparable (77.2%, $P = 0.697$). Proportions were significantly lower in patients with a score < 3.8 at 4 weeks or < 4.6 at baseline. Multivariate logistic regression demonstrated that a DAS28 score of < 3.3 at 12 weeks was an independent strong predictor for LDA at 52 weeks (adjusted odds ratio: 15.2, $P < 0.001$).

Conclusion. Twelve weeks is an adequate observational period to judge the long-term clinical efficacy of abatacept, and is about as early as the period for assessing TNF blockade therapy.

Key words: predictors, adequate observational period, long-term efficacy, abatacept, RA, Japanese, multicentre registry system.

[1]Department of Orthopedic Surgery and Rheumatology, Nagoya University Graduate School of Medicine, Showa-ku, Nagoya, Aichi, Japan, [2]Department of Orthopedic Surgery and Rheumatology, Nagoya Medical Center, Naka-ku, Nagoya, Aichi, [3]Department of Rheumatology, Toyohashi Municipal Hospital, Aotake-cho, Toyohashi, Aichi, [4]Department of Orthopedic Surgery, Konan Kosei Hospital, Takaya-cho, Konan, Aichi, [5]Department of Rheumatology, Tokyo Kosei Nenkin Hospital, Shinjuku-ku, Tokyo, [6]Department of Orthopedic Surgery, Nagoya Central Hospital, Nakamura-ku, Nagoya, Aichi, [7]Department of Orthopedic Surgery, Anjo Kosei Hospital, Anjo, Aichi, [8]Department of Orthopedic Surgery, Ichinomiya Municipal Hospital, Bunkyo, Ichinomiya, Aichi, [9]Kato Orthopedic Clinic, Okazaki, Aichi, [10]Department of Orthopedic Surgery, Kariya-Toyota General Hospital, Kariya, Aichi, [11]Department of Rheumatology, Nagano Red Cross Hospital, Nagano, [12]Department of Orthopedic Surgery, Shizuoka Kosei Hospital, Aoi-ku, Shizuoka, Japan, and [13]Department of Orthopedic Surgery, Toyota Kosei Hospital, Josui-cho, Toyota, Aichi, Japan

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Correspondence to: Nobunori Takahashi, Department of Orthopedic Surgery and Rheumatology, Nagoya University Hospital, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Aichi, 466-8550, Nagoya, Japan.
E-mail: nobunori@med.nagoya-u.ac.jp

Introduction

Abatacept is the first member of a new class of biologic DMARDs for RA that inhibits T-cell activation by binding to CD80/86, modulating its interaction with CD28. The efficacy and safety of abatacept have been reported in several clinical trials [1–3] and in clinical practice [4, 5]. There is a high level of interest in defining predictive factors for the long-term clinical response to abatacept, with the aim of minimizing patient exposure to ineffective therapy; however, only a few studies have assessed this aspect. Our previous study demonstrated that high disease activity at baseline was an independent predictor of clinical response at 24 weeks [6]. Although baseline predictors are of interest, therapy should not be abandoned based on the baseline characteristics of patients in need. There is therefore a great need in medical practice for clinical indices after therapy initiation that can judge and predict the long-term efficacy of abatacept.

Several studies have reported adequate observational periods that predict long-term efficacy of TNF blockade therapies. Van der Cruyssen *et al.* [7] reported that disease activity measured by DAS28 at 14 or 22 weeks of infliximab therapy was the best predictor of long-term attrition. Van der Heijde *et al.* [8] found that failure to achieve improvement in DAS28 within the first 12 weeks of certolizumab pegol therapy independently predicted a low probability of achieving low disease activity (LDA) at 1 year. No similar data currently exist for abatacept.

This study aimed to provide clinical evidence for an adequate observational period that predicts long-term clinical efficacy of abatacept. We determined the prognostic significance of disease activity measured by DAS28-CRP at baseline and after 4, 12 and 24 weeks of abatacept treatment, as well as baseline characteristics, to predict LDA at 52 weeks.

Methods

Participants

All eligible patients were registered in and followed by the Tsurumai Biologics Communication Registry (TBCR) [9]. TBCR was initiated in October 2008 to study the long-term efficacy and safety of biologics used to treat RA. Data were collected retrospectively from 2003 to 2008 and prospectively after 2008. Patient characteristics and disease activity data are available for all RA patients treated with commercially available biologics at TBCR institutes in Japan. Registered data are updated once per year and include drug continuation, reasons for switching drugs and adverse events that may have occurred during treatment.

The present study included all patients who started i.v. abatacept treatment and were prospectively observed for longer than 52 weeks at TBCR-affiliated institutes ($n = 254$). All patients met the 1987 ACR classification criteria for RA. Patients received i.v. abatacept three times at 2-week intervals, and thereafter at 4-week intervals. Patient anonymity was maintained during data collection, and security of personal information was strictly controlled. This study was approved by the Nagoya University Graduate School of Medicine Ethics Committee. Written informed consent was obtained from all participants in this study.

Data collection

Demographic data recorded at initiation of treatment (baseline, week 0) included age, gender, disease duration, RF positivity ($\geqslant$20 IU/ml), history of previous treatment with biological DMARDs, pulmonary comorbidity and concomitant treatment [MTX or prednisolone (PSL)]. Bilateral hand radiographs were used to classify severity of peripheral joint destruction into the four Steinbrocker classification stages I–IV [10]. The following disease parameters were recorded at baseline and after 4, 12, 24 and 52 weeks of treatment: tender joint count and swollen joint count on 28 joints, patient and physician global assessment of disease activity, modified HAQ (mHAQ) score, serum CRP levels and matrix metalloproteinase-3 levels. Disease activity was evaluated at each time point by DAS28-CRP.

The DAS28-CRP is known to underestimate disease activity significantly and overestimate improvement in disease activity significantly compared with the DAS28-ESR [11]. We used different criteria from those for DAS28-ESR. Disease activity was categorized as follows: DAS28-CRP remission (DAS28-CRP < 2.3), LDA ($2.3 \leqslant$ DAS28-CRP < 2.7), moderate disease activity ($2.7 \leqslant$ DAS28-CRP $\leqslant 4.1$) and high disease activity (DAS28-CRP > 4.1). These criteria were defined using a large Japanese cohort study [12].

Statistical analysis

Demographic and disease characteristics are reported using descriptive statistics. All results are expressed as mean (S.D.) or as a percentage. Student's *t*-test was used for two-group comparisons and the Chi-squared test for categorical variables. The last observation carried forward method was used in each analysis.

Receiver operating characteristic (ROC) curves were constructed to determine the best cut-off point for DAS28-CRP at each time point, and the area under the ROC curve (AUC) was calculated as a measure of the overall discriminative ability of the DAS28-CRP score. The cut-off point was identified as the one closest to the (0, 1) point and taken to be the cut-off point that best differentiated between patients with and without LDA achievement at 52 weeks [13].

Multivariate analysis (logistic regression) was performed to determine predictive factors of LDA achievement at 52 weeks. Variables significantly associated with the endpoint in univariate analysis ($P < 0.05$) and the stepwise selection process were used to select the final model. Adjusted odds ratios with 95% CIs were calculated.

All statistical tests were two-sided, and significance was defined as $P < 0.05$. All analyses were performed with SPSS version 20.0.0 software (IBM Corp., Armonk, NY, USA).

Results

Demographic data

A total of 254 patients were enrolled in this study, with four excluded due to incomplete data, giving a final total of 250 patients through October 2013. Mean age was 64.5 (12.3) years, and mean disease duration was 11.3 (12.6) years. Of this cohort, 80.8% were female, 56.4% showed RF positivity, 47.2% had previous biologic DMARD history [mean: 1.6 (0.8)], 48.8% had concomitant MTX treatment [mean dose: 7.4 mg/week (S.D. 2.6)] and 51.2% reported oral steroid usage [mean dose: 4.5 mg/day (S.D. 2.6)]. Of the 250 patients, 176 (70.4%) were categorized into advanced Steinbrocker Stages (III and IV), indicating established RA and joint damage. Mean mHAQ score was 0.70 ± 0.73. Disease activity was high, as shown by a mean DAS28-CRP of 4.50 (1.28) and a mean CRP level of 2.2 mg/dl (S.D. 2.8).

ROC curves

ROC curves for DAS28-CRP at 0, 4, 12 and 24 weeks for achievement of LDA at 52 weeks are shown in Fig. 1A. The AUC and cut-off DAS28-CRP score at each timepoint are also shown. The sensitivity and specificity of each cut-off score was 62.4% and 70.9%, respectively, at baseline, 67.75 and 81.8% at 4 weeks, 79.75 and 81.8% at 12 weeks and 80.55% and 87.3% at 24 weeks. We then compared the DAS28-CRP categorical distribution of disease activity status at 52 weeks between patient groups that achieved the cut-off score at each timepoint. Patients with a DAS28-CRP < 3.0 at 24 weeks also had the highest proportion of LDA achievement at 52 weeks (79.3%) (Fig. 1B). There was no significant difference in the proportion of LDA at 52 weeks for patients with a score of < 3.3 at 12 weeks (77.2%, $P = 0.697$), while proportions were significantly lower for patients with a score of < 3.8 at 4 weeks (67.7%, $P = 0.039$) and those with a score of < 4.6 at baseline (54.6%, $P < 0.001$).

Factors predicting achievement of LDA at 52 weeks

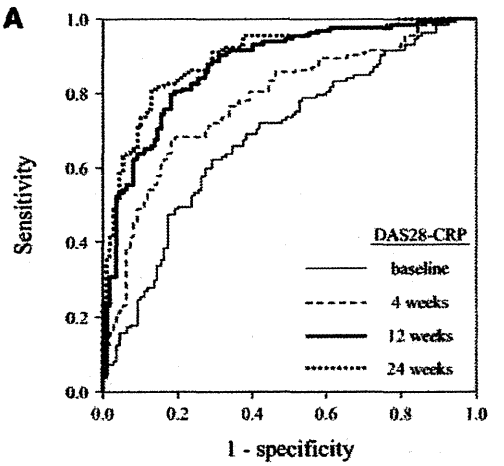
Univariate analysis and multivariate logistic regression were performed to identify predictors of LDA achievement at 52 weeks. Univariate logistic regression showed that the following variables were associated with achievement of LDA at 52 weeks after abatacept initiation: no previous biologic DMARD history, concomitant PSL usage, mHAQ score less than the median value (0.50) and DAS28-CRP score less than the cut-off score (3.3) at 12 weeks (Fig. 2A).

Multivariate logistic regression showed that no previous biologic DMARD history, concomitant PSL and low DAS28-CRP score at 12 weeks were independently associated with achievement of LDA at 52 weeks (Fig. 2B).

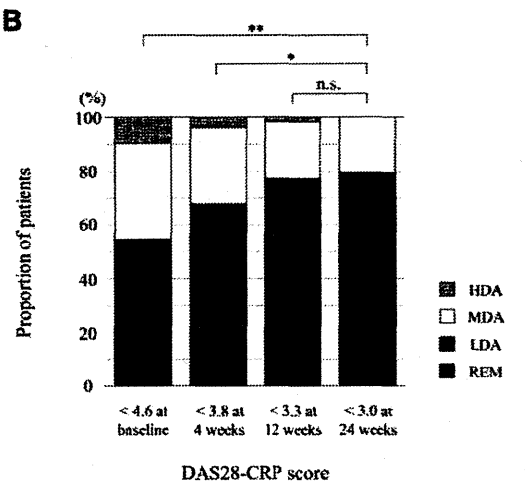
Discussion

Our analysis demonstrates that the predictability of achieving LDA at 52 weeks after starting abatacept therapy is almost equivalent between cut-off DAS28-CRP

Fig. 1 Prognostic significance of disease activity at each timepoint to predict low disease activity at 52 weeks



	AUC	Std. Err.	95% CI	Cut off score
DAS28-CRP				
baseline	0.686	0.034	0.619-0.753	4.6
4 weeks	0.780	0.030	0.721-0.838	3.8
12 weeks	0.875	0.023	0.830-0.919	3.3
24 weeks	0.900	0.020	0.862-0.939	3.0



(**A**) Receiver operating characteristic (ROC) curves of the 28-joint count DAS28-CRP at each time point to predict the achievement of low disease activity (LDA) at 52 weeks after starting abatacept treatment. The table displays the area under the ROC curve (AUC), standard error (S.E.), 95% CI and cut-off DAS28-CRP score for each time point. (**B**) Categorical distribution of disease activity status at 52 weeks in patients with less than each cut-off DAS28-CRP score at each time point. The proportions of patients that achieved LDA at 52 weeks were statistically compared between groups with less than each cut-off score at each time point using the chi-squared test. HDA: high disease activity; MDA: moderate disease activity; LDA: low disease activity; REM: remission, $^*P < 0.05$, $^{**}P < 0.01$.