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

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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. Methotrexate (MTX) is an important anchor drug for RA therapy and should be given as soon as a diagnosis is made. Recommendations from the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 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, and various TNF inhibitors work by halting inflammatory and destructive disease processes. TNF inhibitors in combination with MTX reduce disease activity, slow radiographic progression, and improve function to a greater extent than monotherapies of each agent. 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\textsuperscript{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\textsuperscript{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\textsuperscript{17} and small joints\textsuperscript{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\textsuperscript{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)\textsuperscript{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\textsuperscript{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\textsuperscript{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

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**Image Description:**

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

*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.
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
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, 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.

**REFERENCES**


