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

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

Accepted for publication July 15, 2015.

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

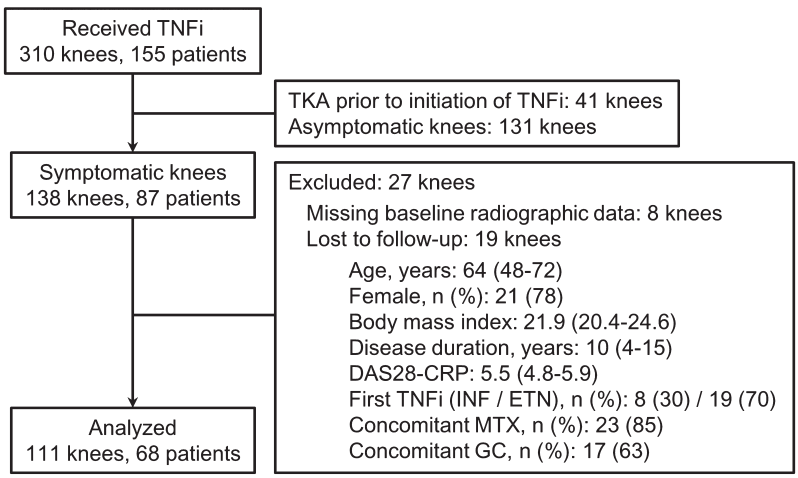

Figure 1. Flowchart depicting the study design. Baseline characteristics of the 27 excluded subjects are presented as median values (interquartile range) or number of subjects (percentage). TNFi: tumor necrosis factor inhibitor; TKA: total knee arthroplasty; DAS28: 28-joint Disease Activity Score; CRP: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

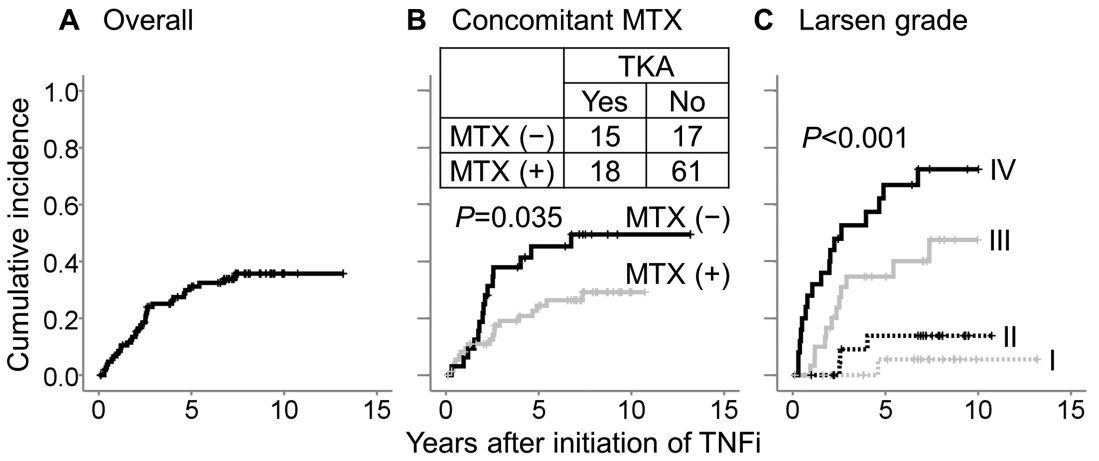

Figure 2. Kaplan-Meier estimates of overall cumulative incidence of TKA (A), and cumulative incidence stratified by concomitant MTX (B) and Larsen grade (C). TNFi: tumor necrosis factor inhibitor; MTX: methotrexate; TKA: total knee arthroplasty.

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.

REFERENCES

1. Breedveld FC, Kalden JR. Appropriate and effective management of rheumatoid arthritis. Ann Rheum Dis 2004;63:627-33.
2. Jacobs JW. Lessons for the use of non-biologic anchor treatments for rheumatoid arthritis in the era of biologic therapies. Rheumatology 2012;51 Suppl 4:iv27-33.
3. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 2012;64:625-39.
4. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492-509.
5. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001;344:907-16.
6. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al; Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000; 343:1594-602.
7. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372:375-82.

8. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al; TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004;363:675-81.
9. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26-37.
10. Emery P, Fleischmann R, van der Heijde D, Keystone EC, Genovese MC, Conaghan PG, et al. The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. Arthritis Rheum 2011;63:1200-10.
11. Keystone E, Heijde Dv, Mason D Jr, Landewé R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008;58:3319-29.
12. Kuper HH, van Leeuwen MA, van Riel PL, Prevoo ML, Houtman PM, Lolkema WF, et al. Radiographic damage in large joints in early rheumatoid arthritis: relationship with radiographic damage in hands and feet, disease activity, and physical disability. Br J Rheumatol 1997;36:855-60.
13. Drossaers-Bakker KW, Kroon HM, Zwinderman AH, Breedveld FC, Hazes JM. Radiographic damage of large joints in long-term rheumatoid arthritis and its relation to function. Rheumatology 2000;39:998-1003.
14. Wolfe F, Zwillich SH. The long-term outcomes of rheumatoid arthritis: a 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. Arthritis Rheum 1998;41:1072-82.
15. James D, Young A, Kulinskaya E, Knight E, Thompson W, Ollier W, et al; Early Rheumatoid Arthritis Study Group (ERAS), UK. Orthopaedic intervention in early rheumatoid arthritis. Occurrence and predictive factors in an inception cohort of 1064 patients followed for 5 years. Rheumatology 2004;43:369-76.
16. Kapetanovic MC, Lindqvist E, Saxne T, Eberhardt K. Orthopaedic surgery in patients with rheumatoid arthritis over 20 years: prevalence and predictive factors of large joint replacement. Ann Rheum Dis 2008;67:1412-6.
17. Imagama T, Tanaka H, Tokushige A, Seki K, Sumiura S, Yamamoto M, et al. Knee joint destruction driven by residual local symptoms after anti-tumor necrosis factor therapy in rheumatoid arthritis. Clin Rheumatol 2013;32:823-8.
18. Aletaha D, Smolen JS. Joint damage in rheumatoid arthritis progresses in remission according to the Disease Activity Score in 28 joints and is driven by residual swollen joints. Arthritis Rheum 2011;63:3702-11.
19. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
20. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis 2009;68:954-60.
21. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn 1977;18:481-91.
22. Guth A, Coste J, Chagnon S, Lacombe P, Paolaggi JB. Reliability of three methods of radiologic assessment in patients with rheumatoid arthritis. Invest Radiol 1995;30:181-5.
23. Seki E, Matsushita I, Sugiyama E, Taki H, Shinoda K, Hounoki H, et al. Radiographic progression in weight-bearing joints of patients with rheumatoid arthritis after TNF-blocking therapies. Clin Rheumatol 2009;28:453-60.
24. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2009;68:1086-93.
25. Burmester GR, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL, et al. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Ann Rheum Dis 2015;74:1037-44.
26. Kameda H, Kanbe K, Sato E, Ueki Y, Saito K, Nagaoka S, et al. Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. J Rheumatol 2011;38:1585-92.
27. Kameda H, Kanbe K, Sato E, Ueki Y, Saito K, Nagaoka S, et al; Japan Biological Agent Integrated Consortium (JBASIC). A merged presentation of clinical and radiographic data using probability plots in a clinical trial, the JESMR study. Ann Rheum Dis 2013;72:310-2.
28. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of 7740 patients. Mod Rheumatol 2014;24:390-8.
29. Leon L, Abasolo L, Carmona L, Rodriguez-Rodriguez L, Lamas JR, Hernandez-Garcia C, et al; emAR Study Group. Orthopedic surgery in rheumatoid arthritis in the era of biologic therapy. J Rheumatol 2013;40:1850-5.
30. Eckstein F, Kwoh CK, Boudreau RM, Wang Z, Hannon MJ, Cotofana S, et al; OAI investigators. Quantitative MRI measures of cartilage predict knee replacement: a case-control study from the Osteoarthritis Initiative. Ann Rheum Dis 2013;72:707-14.
31. Jämsen E, Huhtala H, Puolakka T, Moilanen T. Risk factors for infection after knee arthroplasty. A register-based analysis of 43,149 cases. J Bone Joint Surg Am 2009;91:38-47.
32. Himanen AK, Belt EA, Lehto MU, Hämäläinen MM. A comparison of survival of moulded monoblock and modular tibial components of 751 AGC total knee replacements in the treatment of rheumatoid arthritis. J Bone Joint Surg Br 2007;89:609-14.