# Simultaneous Treatment with Subcutaneous Injection of Golimumab and Intra-articular Injection of Triamcinolone Acetonide (K-Method) in Patients with Rheumatoid Arthritis Undergoing Switching of Biologics: Retrospective Case–Control Study

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**ABSTRACT**

**BACKGROUND:** Tight control of severe rheumatoid arthritis (RA) in patients with high disease activity, even when using biologics, is sometimes difficult using a treat-to-target strategy. Switching from one biologic to another is associated with lower efficacy than that in treatment-naive cases. We developed the K-method that involves simultaneous treatment with golimumab and intra-articular joint injection of triamcinolone acetonide (TA) in patients undergoing switching of biologics. We performed this retrospective case–control study to investigate the efficacy of achieving an immediate treatment response using the K-method.

**METHODS:** This study involved 20 patients with RA (control group, 10 patients; K-method group, 10 patients). Patients in the control group were switched to golimumab from other biologics without intra-articular injection of TA. The K-method involved injection of 1 mL of TA (40 mg/mL) and 2 mL of 1% lidocaine hydrochloride into swollen or painful joints on the same day as golimumab treatment. A quick response one day after treatment was compared between the two groups according to the disease activity score 28 based on C-reactive protein (DAS28 CRP), clinical disease activity index (CDAI), simplified disease activity index (SDAI), European League Against Rheumatism (EULAR) response, and remission rate. These parameters were investigated for 24 weeks.

**RESULTS:** The K-method group showed significant improvements in DAS28 CRP, CDAI, and SDAI at one day, 12 weeks, and 24 weeks compared with the control group. The number of swollen and tender joints and the patient and doctor global visual analog scale scores were also significantly different between the two groups. The remission rates based on DAS28 CRP were 30% at one day, 50% at 12 weeks, and 60% at 24 weeks in the K-method group. The EULAR good/moderate response rates were 80% at one day, 90% at 12 weeks, and 90% at 24 weeks in the K-method group; however, these rates were only 10%, 40%, and 40%, respectively, in the control group. No adverse events occurred in either group.

**CONCLUSION:** Simultaneous treatment with biologics and intra-articular injection of TA is useful for cases involving switching of biologics for RA. This strategy is safe and practical for RA treatment.

**KEYWORDS:** biologics, injection, rheumatoid arthritis, triamcinolone acetonide

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## Background

The ultimate goal of medical treatment of rheumatoid arthritis (RA) is to achieve a state of remission or low disease activity (LDA) by a strategy called treat-to-target.[1] In practice, clinical remission infrequently occurs after toleration of biologic treatment; however, ongoing therapy with disease-modifying antirheumatic drugs or other biologic agents may be required. Switching among biologic agents is often performed in patients who do not respond to one or more biologics. However, in patients with high disease activity, it is reported that the effects of biologics are lower than those in treatment-naive patients.[2] Conversely, intra-articular injection of corticosteroids for treatment of RA-induced synovitis was reported in a randomized controlled study.[3] Triamcinolone acetonide (TA), one of these corticosteroids, has a long duration of action and is preferable for mid-sized to large joints.[4] The Optimized Treatment Algorithm in Early Rheumatoid Arthritis (OPERA) study recently reported that combination therapy involving intra-articular injection of triamcinolone hexacetonide and subcutaneous injection of the biologic reagent adalimumab increased the remission rate, function, and quality of life in patients with early RA.[5] However, the OPERA study

did not state whether the triamcinolone hexacetonide and adalimumab were administered on the same day. Furthermore, the effect of simultaneous therapy with TA and a biologic reagent has not been reported in cases involving switching of biologics, especially in patients with high disease activity.

We have found that intra-articular injection of TA and administration of biologics on the same day (ie, the K-method) induce an extremely quick response in cases involving switching of biologics. We performed a retrospective case–control study to preliminarily analyze the effect of the K-method.

## Methods

**Study design and data collection.** Twenty patients who fulfilled the 1987 American College of Rheumatology revised criteria for RA[6] were enrolled in this retrospective case–control study. The patients were divided into a control group (10 patients) and a K-method group (10 patients). The clinical characteristics of the patients in each group are shown in Table 1. A Steinbrocker stage of I, II, III, and IV was seen in zero, one, four, and five patients in the control group and in zero, three, three, and four patients in the K-method group, respectively.[7] A Steinbrocker class of 1, 2, 3, and 4 was seen in zero, one, nine, and zero patients in the control group and in zero, three, seven, and zero patients in the K-method group, respectively.[7] Patients in the control group were switched to golimumab from other biologics without intra-articular injection of TA. The selection method was not randomized in this study. Control patients were selected from September 2012 to August 2013 before starting the K-method. Patients who underwent the K-method were selected from September 2013 to June 2014. The inclusion criteria were high disease activity (disease activity score 28 based on C-reactive protein [DAS28 CRP] >5.0) and a history of using biologics other than golimumab. Before using golimumab, three patients in the control group had been treated with etanercept, three with tocilizumab, three with abatacept, and one with infliximab. In the K-method group, four patients had been treated with etanercept, three with tocilizumab, and three with abatacept. All patients included were of first-switch cases from other biologics to golimumab. The exclusion criteria were LDA, remission, and biologics naive. This research complied with the principles of the Declaration of Helsinki. Informed consent was obtained from all the patients, and the study protocol was approved by the ethics committee of Tokyo Women's Medical University (approval number 3319). The primary outcome was the proportion of patients in each group who achieved LDA (DAS28 CRP <3.2) at 24 weeks. The secondary outcomes were the DAS28 CRP and proportions of patients who achieved DAS28 remission (DAS28 CRP <2.6) and an American College of Rheumatology/European League Against Rheumatism (EULAR) good/moderate response at 24 weeks.[8] The dose of golimumab was 100 mg in 70% of patients in both the groups because of patients' financial concerns. No significant differences were present in the baseline clinical data between the two groups (Table 1). The presence of a quick response at one day was compared between the K-method and control groups based on the DAS28 CRP, clinical disease activity index (CDAI), simplified disease activity index (SDAI), EULAR response, and remission rate. These parameters were evaluated for 24 weeks.

**K-method.** The K-method involved intra-articular injection of 1 mL of TA (Kenacort-A®; Bristol-Myers Squibb Company; 40 mg/mL) and 2 mL of 1% lidocaine hydrochloride (Xylocaine®; AstraZeneca) into the most swollen or painful joints (ie, only one large joint was injected per patient per treatment) on the same day as golimumab treatment. TA injection was indicated for only one of the following large joints at a time, even when the bilateral joints were swollen: knee, shoulder, elbow, wrist, or ankle. TA injection was performed in up to three swollen finger joints using a total of 3 mL divided among

**Table 1.** Baseline demographic, clinical and laboratory characteristics of the study population.

| | CONTROL GROUP (n = 10) | K-METHOD GROUP (n = 10) | *P* VALUE |
|---|---|---|---|
| Age (years) | 64.6 ± 8.98 | 70.5 ± 10.5 | 0.095 |
| Female sex (%) | 70 | 90 | 0.276 |
| Disease duration (years) | 17.6 ± 12.5 | 11.2 ± 10.2 | 0.150 |
| MTX %/dose of MTX (mg/week) | 60/7.3 ± 0.4 (8–12) | 50/7.6 ± 0.3 (6–12) | 0.661 |
| PSL %/dose of PSL (mg/day) | 50/4.2 ± 1.17 | 60/3.29 ± 1.09 | 0.661 |
| DAS28 (CRP) | 5.71 ± 0.63 | 5.94 ± 0.60 | 0.325 |
| CRP (mg/dl) | 3.25 ± 1.75 | 4.13 ± 3.95 | 0.705 |
| RF positive (%) | 100 | 90 | 0.317 |
| Anti-CCP positive (%) | 60 | 70 | 0.648 |
| Number of tender joints (0–40) | 9.2 ± 3.43 | 11.4 ± 4.01 | 0.157 |
| Number of swollen joints (0–40) | 9.8 ± 4.05 | 12.2 ± 3.43 | 0.217 |
| VAS-patient global (0–100 mm) | 72.2 ± 9.98 | 66.0 ± 10.5 | 0.232 |
| VAS-doctors global (0–100 mm) | 72.5 ± 8.58 | 71.0 ± 13.1 | 0.938 |

**Note:** *P* Values for differences between two treatment groups by Mann-Whitney U test or Fisher's exact test.
**Abbreviations:** Anti-CCP, anticyclic citrullinated protein antibodies; DAS28 (CRP), Disease Activity Score; VAS, visual analogue scale.

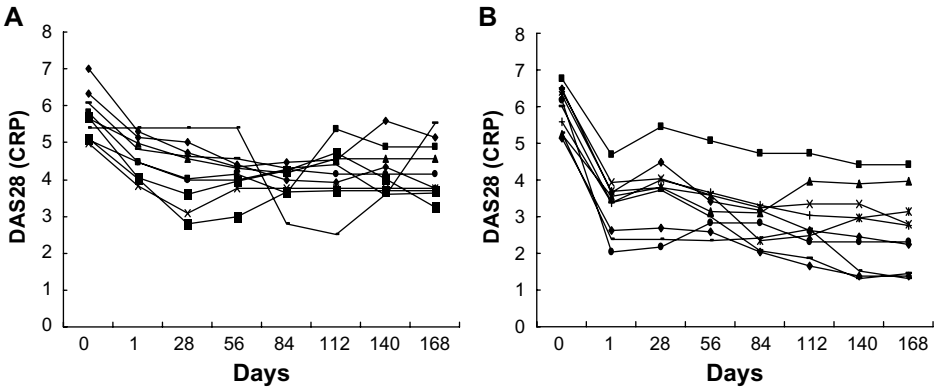


**Figure 1.** Changes in DAS23 CRP scores from one day to 24 weeks: (**A**) control group and (**B**) K-method group.

all injected finger joints (1 mL of TA and 2 mL of 1% lidocaine hydrochloride). The exclusion criteria for intra-articular injection were bacterial infection and severe diabetes mellitus. As an example of this protocol, the TA was injected into the right knee and 50 mg of golimumab was then injected subcutaneously within one hour. K stands for Kanbe or Kenakort-A®. K-method includes other biologics except golimumab.

**Statistical analysis.** The Wilcoxon signed-rank test was used to compare the DAS28 CRP at baseline, one day, and 24 weeks using the IBM SPSS Statistics 15 software program (International Business Machines Corp.). Comparisons between the two groups were made using the Fisher's exact test and the Mann–Whitney *U* test. All patients reached the 24-week end point without discontinuation of treatment. The data are presented as mean ± standard deviation. A *P*-value of $<0.05$ was considered statistically significant.

## Results

Figure 1 shows the changes in the DAS28 CRP scores from one day to 24 weeks in each group. The DAS28 CRP was significantly lower throughout the 24-week study duration than that at baseline in both the groups (control group: $P = 0.007$, 0.008, 0.008, 0.005, 0.005, 0.005, and 0.005 at one day, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, and 24 weeks, respectively; K-method group: $P = 0.007$, 0.008, 0.008, 0.005, 0.005, 0.005, and 0.005 at one day, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, and 24 weeks, respectively; Fig. 1).

One day after treatment, the control and K-method groups exhibited a DAS28 CRP of 4.64 ± 0.57 and 3.34 ± 0.79 mg/dL ($P = 0.001$), CDAI of 16.70 ± 3.56 and 6.21 ± 2.84 mg/dL ($P < 0.001$), SDAI of 18.90 ± 0.57 and 8.21 ± 4.21 mg/dL ($P < 0.001$), and CRP of 2.23 ± 2.52 and 2.01 ± 1.78 mg/dL ($P = 0.971$), respectively (Table 2). The number of tender joints, number of swollen joints, patient global visual analog scale (VAS) score, and doctor global VAS score were all significantly different between the two groups. The remission rate (DAS28 CRP <2.6) was 30% in the K-method group and 0% in the control group ($P = 0.067$). The LDA of DAS28 CRP was 50% in the K-method group and 0% in the control group ($P = 0.012$).

**Table 2.** Treatment responses and remission rates after 1 day.

| | CONTROL GROUP (n = 10) | K-METHOD GROUP (n = 10) | *P* VALUE |
|---|---|---|---|
| DAS28 (CRP) | 4.64 ± 0.57 | 3.34 ± 0.79 | 0.001 |
| CDAI | 16.7 ± 3.56 | 6.21 ± 2.84 | <0.001 |
| SDAI | 18.9 ± 0.57 | 8.21 ± 4.21 | <0.001 |
| CRP (mg/dl) | 2.23 ± 2.52 | 2.01 ± 1.78 | 0.971 |
| Number of tender joints (0–40) | 6.40 ± 1.84 | 2.50 ± 1.51 | <0.001 |
| Number of swollen joints (0–40) | 6.98 ± 2.59 | 2.20 ± 0.92 | <0.001 |
| VAS-patient global (0–100 mm) | 52.2 ± 8.43 | 15.1 ± 7.71 | <0.001 |
| VAS-doctors global (0–100 mm) | 62.2 ± 9.67 | 14.7 ± 7.19 | <0.001 |
| DAS28 (CRP) <2.6 (%) | 0 | 30 | 0.067 |
| DAS28 (CRP) <3.2 (%) | 0 | 50 | 0.012 |
| EULAR good/moderate response | 0/1 | 2/6 | 0.002 |

**Note:** *P* Values for differences between two treatment groups by Mann-Whitney U test or Fisher's exact test.
**Abbreviations:** DAS28 (CRP), Disease Activity Score, 28 joints, CRP based; CRP, C-reactive protein; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index; VAS, Visual Analogue Scale; EULAR, European League Against Rheumatism.

**Table 3.** Treatment responses and remission rates after 12 weeks.

| | CONTROL GROUP (n = 10) | K-METHOD GROUP (n = 10) | *P* VALUE |
|---|---|---|---|
| DAS28 (CRP) | 3.95 ± 0.50 | 2.91 ± 0.80 | 0.005 |
| CDAI | 9.0 ± 3.29 | 5.01 ± 4.01 | 0.029 |
| SDAI | 13.0 ± 3.89 | 6.79 ± 4.91 | 0.004 |
| CRP (mg/dl) | 4.03 ± 4.63 | 1.68 ± 1.77 | 0.218 |
| Number of tender joints (0–40) | 2.80 ± 1.03 | 1.60 ± 1.95 | 0.043 |
| Number of swollen joints (0–40) | 2.90 ± 1.1 | 1.80 ± 1.67 | 0.035 |
| VAS-patient global (0–100 mm) | 33.0 ± 14.9 | 17.0 ± 8.23 | 0.011 |
| VAS-doctors global (0–100 mm) | 38.9 ± 12.3 | 18.0 ± 9.49 | 0.023 |
| DAS28 (CRP) <2.6 (%) | 10 | 50 | 0.057 |
| DAS28 (CRP) <3.2 (%) | 20 | 80 | 0.009 |
| EULAR good/moderate response | 1/3 | 4/5 | 0.022 |

**Note:** *P* Values for differences between two treatment groups by Mann-Whitney U test or Fisher's exact test.
**Abbreviations:** DAS28 (CRP), Disease Activity Score,28 joints, CRP based; CRP, C-reactive protein; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index; VAS, Visual Analogue Scale; EULAR, European League Against Rheumatism.

The EULAR good/moderate responses were observed in 80% of patients in the K-method group and in 10% of the control group patients ($P < 0.001$; Table 2).

At 12 weeks, the control and K-method groups exhibited a DAS28 CRP of 3.95 ± 0.50 and 2.91 ± 0.80 mg/dL ($P = 0.005$), CDAI of 9.00 ± 3.29 and 5.01 ± 4.01 mg/dL ($P = 0.029$), SDAI of 13.00 ± 3.89 and 6.79 ± 4.91 mg/dL ($P = 0.004$), and CRP of 4.03 ± 4.63 and 1.68 ± 1.77 mg/dL ($P = 0.218$), respectively (Table 3). The number of tender joints, number of swollen joints, patient global VAS score, and doctor global VAS score were all significantly different. The remission rate (DAS28 CRP < 2.6) was 50% in the K-method group and 10% in the control group. The LDA of DAS28 CRP was 80% in the K-method group and 20% in the control group. The EULAR good/moderate responses were observed in 90% of patients in the K-method group and in 40% of the control group patients (Table 3).

At 24 weeks, the control and K-method groups exhibited a DAS28 CRP of 4.23 ± 0.75 and 2.56 ± 1.07 mg/dL ($P = 0.002$), CDAI of 12.00 ± 5.83 and 4.25 ± 3.39 mg/dL ($P = 0.005$), SDAI of 15.10 ± 6.06 and 5.51 ± 4.74 mg/dL ($P = 0.001$), and CRP of 2.96 ± 3.41 and 1.28 ± 1.78 mg/dL ($P = 0.052$), respectively (Table 4). The number of tender joints, number of swollen joints, patient global VAS score, and doctor global VAS score were all significantly different. The remission rate (DAS28 CRP < 2.6) was 60% in the K-method group and 0% in the control group. The LDA of DAS28 CRP was 80% in the K-method group and 30% in the control group. The EULAR good/moderate responses were observed in 80% of patients in the K-method group and in 40% of the control group patients. The discontinuation rate at 24 weeks was 30% in the control group and 0% in the K-method group. Three patients who discontinued treatment were switched to other biologics, and three were switched

**Table 4.** Treatment responses and remission rates after 24 weeks.

| | CONTROL GROUP (n = 10) | K-METHOD GROUP (n = 10) | *P* VALUE |
|---|---|---|---|
| DAS28 (CRP) | 4.23 ± 0.75 | 2.56 ± 1.07 | 0.002 |
| CDAI | 12.0 ± 5.83 | 4.25 ± 3.39 | 0.005 |
| SDAI | 15.1 ± 6.06 | 5.51 ± 4.74 | 0.001 |
| CRP (mg/dl) | 2.96 ± 3.41 | 1.28 ± 1.78 | 0.052 |
| Number of tender joints (0–40) | 8.0 ± 3.1 | 1.20 ± 1.39 | 0.005 |
| Number of swollen joints (0–40) | 6.0 ± 3.8 | 1.50 ± 1.35 | 0.019 |
| VAS-patient global (0–100 mm) | 40.2 ± 15.5 | 15.5 ± 10.1 | 0.001 |
| VAS-doctors global (0–100 mm) | 44.6 ± 11.7 | 19.5 ± 13.0 | 0.004 |
| DAS28 (CRP) <2.6 (%) | 0 | 60 | 0.004 |
| DAS28 (CRP) <3.2 (%) | 30 | 80 | 0.028 |
| EULAR good/moderate response | 0/4 | 5/4 | 0.022 |

**Notes:** *P* Values for differences between two treatment groups by Mann-Whitney U test or Fisher's exact test.
**Abbreviations:** DAS28(CRP), Disease Activity Score,28 joints, CRP based; CRP, C-reactive protein; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index; VAS, Visual Analogue Scale; EULAR, European League Against Rheumatism.

to the K-method to achieve LDA. No adverse events occurred in either group.

## Discussion

Intra-articular injection of corticosteroids is accepted by patients with RA whose joints are swollen and painful. However, corticosteroid injections alone are insufficient to control the systemic inflammation associated with RA. We previously reported that arthroscopic synovectomy improved the DAS28 CRP in patients who tolerated infliximab.[9] Thus, local synovial inflammation may play an important role in the systemic pathogenesis of RA. The corticosteroid TA may suppress local synovitis and facilitate the response to golimumab by a booster effect that persists long after intra-articular injection. Simultaneous therapy with golimumab and TA on the same day, namely, the K-method, is effective in cases involving the switching of biologics, even for patients with very high disease activity as in the present case–control study. No reports have described treatment efficacy one day after administration of biologics. The K-method led to a 30% remission rate, 50% LDA rate, and 80% EULAR good/moderate response rate, showing a quicker treatment response than that in the control group. These results indicate that intra-articular injection of TA on the same day as golimumab treatment is an extremely valuable therapeutic strategy in patients with RA. In one study, aggressive intervention with methotrexate combined with glucocorticoid injections into swollen joints effectively controlled disease activity and halted radiographic progression over five years of follow-up in patients with early RA.[10] This low-cost strategy yielded results comparable with those reported for biologics as first-line therapy.[11] Thus, it has been speculated that these favorable results are attributable to a treat-to-target strategy rather than the superiority of any specific drug.[12]

The limitations in the present study included the retrospective case–control nature and the small number of patients with very high disease activity (DAS28 CRP $>$ 5.0), in addition to the examination one day after treatment in patients undergoing switching of biologics; thus, it was difficult to enroll patients for this case–control study. A double-blind randomized controlled trial of the effects of the K-method is required to confirm the possibility of achieving a high remission rate and quick response for patients who tolerate biologics.

## Conclusions

Simultaneous treatment with biologics and intra-articular injection of TA is useful for cases involving switching of biologics for RA. This strategy is safe and practical for clinical RA treatment. It achieves a quick treatment response and a high rate of EULAR good/moderate responses in one day.

## Author Contributions

Designed the study: KK, JC, MT. Acquired the data: KK, JC, YI, TD. Performed the statistical analyses: KK. Drafted the manuscript: KK. Critically revised the manuscript: JC, YI, TD, MT, AY. All the authors read and approved the final manuscript.

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