*Original Article*

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# Switching from originator infliximab to biosimilar infliximab in Japanese patients with rheumatoid arthritis achieving clinical remission (the IFX-SIRIUS study I): An interventional, multicenter, open-label, single-arm clinical trial with clinical, ultrasound and biomarker assessments

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**SUMMARY**: Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by the presence of autoantibodies, with infliximab (IFX), the first biological disease-modifying anti-rheumatic drug (DMARD) targeting tumor necrosis factor α, significantly improving treatment but prompting the development of cost-effective biosimilar DMARDs due to its high cost. This study aimed to investigate the efficacy and safety of switching from originator to biosimilar IFX, CT-P13, in patients with RA using musculoskeletal ultrasound (MSUS) and clinical disease activity indices. This prospective, open-label, interventional, single-arm clinical trial involved a 24-week follow-up, enrolling patients with RA who had achieved clinical remission during treatment with originator IFX. CT-P13 was switched from the originator IFX with an unchanged dosing regimen for 24 weeks. The study utilized not only clinical disease activity indices but also MSUS and serum cytokines/chemokines. Eighteen patients were evaluated during the study period. From baseline to week 24, two of the 18 patients experienced clinical relapse (11.1% [95% CI: 3.1–32.8]). No changes were observed in the MSUS score, including total grayscale and power Doppler scores, Disease Activity Score 28 (DAS28)-erythrocyte sedimentation rate, DAS28-C-reactive protein, Health Assessment Questionnaire-Disability Index, and van der Heijde-modified total Sharp score from baseline to week 24. Serum levels of multiple cytokines/chemokines showed no apparent changes. Three non-serious adverse events occurred, with no study discontinuations due to adverse events. In conclusion, most RA patients undergoing treatment with originator IFX in clinical remission could safely switch to CT-P13 without an increased risk of relapse, as evidenced by MSUS, clinical indices, and biomarker levels.

***Keywords***: rheumatoid arthritis, biosimilar, CT-P13, musculoskeletal ultrasound, biomarker

## 1. Introduction

Rheumatoid arthritis (RA) is characterized by persistent synovitis, systemic inflammation, and autoantibodies (*1*). Uncontrolled active RA leads to joint damage, dis-ability, reduced quality of life, and comorbidities. Therefore, tight control of disease activity using the treat-to-target strategy is recommended (*2*). Advances in RA treatment, including biological disease-modifying anti-rheumatic drugs (bDMARDs), have improved clinical outcomes, such as achieving clinical remission. Clinicians also aim for imaging and immunological remission (*3*).

RA pathophysiology involves multiple inflammatory cascades, notably the over-production and overexpression of tumor necrosis factor (TNF), which drives synovial inflammation and joint destruction (*1*). Infliximab (IFX), a chimeric monoclonal antibody targeting TNF-α, was the first bDMARD to significantly alter RA's course/prognosis, effectively suppressing disease activity and joint destruction progression (*4-6*). However, the high cost of bDMARDs imposes a significant financial burden, making it difficult for certain patients to begin or maintain these therapies. Consequently, biosimilar DMARDs (bsDMARDs) have emerged as cost-effective alternatives that reduce the economic burden. A "biosimilar" is a biotherapeutic product comparable in quality, safety, and efficacy to a licensed reference biotherapeutic product (*i.e.*, originator).

CT-P13, developed by Celltrion (Incheon, South Korea), was approved in 2014 as the first bsDMARD for RA treatment in Japan (*7*). The biosimilar CT-P13 and originator IFX have been shown to be pharmacokinetically equivalent with comparable efficacy and safety (*7*). Previous studies have reported that switching from originator IFX to CT-P13 maintained clinical efficacy (*8,9*). However, previous research relied on clinical disease activity indices as efficacy endpoints without utilizing high-sensitivity imaging modalities, such as joint musculoskeletal ultrasound (MSUS), to assess disease activity.

MSUS is primarily used to evaluate RA disease activity (*10,11*). MSUS is recommended for its superior visualization of synovial inflammation compared with clinical examination (*10,11*). Employing MSUS to assess therapeutic response can be highly beneficial in clinical practice (*10-13*). MSUS is a non-invasive, objective, cost-effective, and reproducible imaging modality ideal for treatment monitoring (*10,11*). Although clinical remission can be achieved in a relatively large number of patients with RA by introducing bDMARD therapy, residual synovitis detected by MSUS remains at a certain frequency, even in patients who achieve clinical remission (*14,15*). Residual synovitis is an important finding that can predict joint destruction and clinical relapse. Therefore, it is important to accurately evaluate disease activity at the joint level using MSUS, as well as clinical disease activity indices, including subjective parameters.

This study evaluated the impact of switching from originator IFX to CT-P13 using MSUS as well as clinical disease activity indices so that the patients' disease activity could be more accurately assessed.

## 2. Materials and Methods

### 2.1. Study design

This study was a prospective, open-label, interventional, single-arm clinical trial. The study was conducted at the following 19 centers: Nagasaki University Hospital, Asahi General Hospital, Chiba-East Hospital, Eiraku Clinic, Fukushima Medical University Hospital, Hamanomachi Hospital, Japanese Red Cross Nagasaki Genbaku Hospital, Kagawa University Hospital, Kindai University Hospital, University of Miyazaki Hospital, Miyazaki Zenjinkai Hospital, Nagasaki Kita Hospital, Osaka Metropolitan University Hospital, Osaka Medical and Pharmaceutical University Hospital, Sagawa Akira Rheumatology Clinic, Sasebo Chuo Hospital, Tobata General Hospital, Utazu Hospital, and Yoshitama Clinic for Rheumatic Diseases. This study was registered in the Japan Registry of Clinical Trials (*https://jrct.niph.go.jp*) as jRCTs071190030. The study has been approved by the certified review board of Nagasaki University. The reference number was CRB19-010. Written informed consent was provided by patients before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki (*16*), the Clinical Trials Act (since February 2019), the Act on the Protection of Personal Information and related regulatory notifications, and this clinical study protocol. The protocol for this study was previously published (*17*).

### 2.2. Patients

The inclusion criteria were (1) age ≥ 20 years, (2) diagnosis of RA based on the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 RA Classification Criteria (*18*); (3) treatment with originator IFX for ≥ 24 weeks and achieving clinical remission defined as a Disease Activity Score 28 (DAS28)-erythrocyte sedimentation rate (ESR) < 2.6 at the last administration of originator IFX and at baseline; and (4) able and willing to give written informed consent and comply with the requirements of the study protocol.

The exclusion criteria were (1) concurrent use of a glucocorticoid equivalent to > 10 mg/day of prednisolone; (2) previous use of a biosimilar for IFX; (3) treatment with a bDMARD other than originator IFX, a bsDMARD, or a Janus kinase (JAK) inhibitor at the baseline visit; (4) a history of infusion reaction due to originator IFX that required medication; (5) treatment with a glucocorticoid or conventional synthetic

DMARDs and changed the dose within 8 weeks prior to the baseline visit; (6) use of a prohibited drug or therapy within 8 weeks prior to the baseline visit; (7) current pregnancy, breastfeeding, or noncompliance with a medically approved contraceptive regimen during and 6 months after the study period; or (8) being considered unsuitable for this study by the investigator.

2.3. Intervention

CT-P13 was administered at the same dose (dose per kg) and the same interval as the originator IFX before switching with an unchanged dosing regimen for 24 weeks. All patients had to continue to take the same doses of methotrexate (MTX) and oral glucocorticoids that they were taking before the switch throughout the study period. During the study period, the following treatments were prohibited: administration of a bDMARD or JAK inhibitor, the concomitant use of an immunosuppressant (azathioprine, cyclophosphamide, or cyclosporine) or oral glucocorticoids equivalent to > 10 mg/day of prednisolone (PSL), intra-articular corticosteroid injections at joints, and non-steroidal anti-inflammatory drugs (NSAIDs) suppositories. During the study period, the dosage of any NSAID could be modified within the range of its approved doses in Japan.

If a patient experienced a clinical relapse, the patient was discontinued from this study. Clinical relapse was defined as (1) a change from the baseline value in the DAS28-ESR (ΔDAS28-ESR) ≥ 1.2 or in the DAS28-ESR ≥ 3.2, and (2) an increase in the DAS28-ESR value due to elevated disease activity of RA, rather than other factors.

2.4. Outcome measurements

The study visits took place at baseline and after 12 and 24 weeks of treatment, respectively. These assessments are shown in Supplementary Figure S1 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=268*). The clinical assessors were blinded to joint assessments using MSUS.

Clinical disease activity was evaluated by each attending physician (Japan College of Rheumatology [JCR]-certified rheumatologists) based on the values of the DAS28-ESR and DAS28-C-reactive protein (CRP) (*19*). The patients' functional assessment was evaluated using the Health Assessment Questionnaire-Disability Index (HAQ-DI) (*20*).

The participants underwent MSUS imaging at baseline, week 12, and week 24. MSUS examinations for each patient were performed by one of the JCR-certified sonographers, defined as having at least one year of MSUS experience and practical experience with more than 50 cases. A systematic multiplanar grayscale (GS) and power Doppler (PD) examination of each patient's joint was performed using a multifrequency linear transducer (12–24 MHz). PD was used depending on which Doppler modality was the most sensitive on the individual machines. The Doppler settings were adjusted at each hospital according to published recommendations (*21*). There were no changes in the MSUS settings during the study and no software upgrades. Joint synovitis was assessed by MSUS at dorsal views of 22 joints: bilateral wrist joints, 1st–5th metacarpophalangeal (MCP) joints, the interphalangeal (IP) joints, and the 2nd–5th proximal interphalangeal (PIP) joints. Each joint was scored for GS and PD on a scale from 0 to 3 in a semi-quantitative manner. The sum of the GS and PD scores was considered the total GS and PD scores, respectively. We also assessed the Global Outcome Measures in Rheumatology (OMERACT)-EULAR Synovitis Score (GLOESS) (*22,23*). GLOESS has been combined with synovial hypertrophy, as shown by GS and PD.

X-ray images of bilateral hands and feet were conducted at posteroanterior and anteroposterior views, respectively. Trained JCR-certified rheumatologists (T.K. and T.S.) evaluated joint damage progression based on the van der Heijde-modified total Sharp score (vdH-mTSS) method as previously described (*24*), including 16 areas in each hand for erosions and 15 for joint-space narrowing (*25*).

2.5. Biomarker measurements

The serum concentrations of the following biomarkers were measured. Rheumatoid factor (RF) was measured by a latex agglutination turbidimetric immunoassay (LTIA) (LZ test "Eiken" RF) (Eiken Chemical Co., Ltd., Tokyo, Japan). Anti-cyclic citrullinated peptide antibodies (ACPA) were measured by a chemiluminescent enzyme immunoassay (CLEIA) (STACIA MEBLux test CCP) (Medical & Biological Laboratories Co., Ltd., Tokyo, Japan). Matrix metalloproteinase-3 (MMP-3) was measured by a latex turbidimetric immunoassay (LTIA) (Panaclear MMP-3 "Latex") (Sekisui Medical Co., Ltd., Tokyo, Japan). Multiplex cytokine/chemokine bead assays were performed using diluted serum supernatants and a MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel (Merck KGaA, Darmstadt, Germany). Bio-Plex Pro Human Cytokine Assays (Bio-Rad, Hercules, CA) were analyzed with a Bio-Plex MAGPIX™ Multiplex Reader (Bio-Rad) according to the manufacturer's instructions.

The cytokines/chemokines that were measured by the bead panel include inter-leukin (IL)-1α, IL-1β, IL-1 receptor antagonist, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17, IL-18, interferon-gamma (IFN-γ), IFN-α2, CXCL1 (growth-related oncogene [GRO]), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), CX3CL1 (fractalkine), flt-3 ligand, fibroblast growth factor (FGF)-2, eotaxin, epidermal growth

factor (EGF), soluble CD40 ligand (sCD40L), vascular endothelial growth factor (VEGF), TNF-β, TNF-α, transforming growth factor (TGF)-α, CCL4 (macrophage inflammatory protein [MIP]-1β), CCL3 (MIP-1α), CCL22 (macrophage-derived chemokine [MDC]), CCL7 (monocyte chemotactic protein [MCP]-3), CCL2 (MCP-1), CXCL10 (IFN-γ-inducible protein [IP]-10), vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1). Serum levels of IL-6 and TNFα were measured using specific enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN).

### 2.6. Study endpoints

The primary endpoint was the proportion of patients who experienced a clinical relapse during the period from baseline to week 24. Clinical relapse was defined as (1) a change from the baseline value in the DAS28-ESR (ΔDAS28-ESR) ≥ 1.2 or in the DAS28-ESR ≥ 3.2, and (2) an increase in the DAS28-ESR value due to elevated disease activity of RA, rather than other factors.

The secondary endpoints of this study were as follows: (1) the proportion of patients who experienced a clinical relapse during the period from baseline to week 12, (2) changes in the total PD and GS scores and the GLOESS from baseline to weeks 12 and 24, (3) the changes in the DAS28-ESR and DAS28-CRP values from baseline to weeks 12 and 24, (4) the change in vdH-mTSS from baseline to week 24, (5) the change in the HAQ-DI score from baseline to weeks 12 and 24, and (6) the changes in the serum levels of biomarkers from baseline to weeks 12 and 24. In addition, the safety endpoint was an occurrence of adverse events.

### 2.7. Statistical analysis method

The non-inferiority margin and sample size determination are described in detail in the protocol for this study (*17*). Briefly, this study aimed to test the non-inferiority of CT-P13 to the originator IFX, using a non-inferiority margin based on two clinical studies (*26,27*). The null hypothesis for noninferiority was rejected if the upper boundary of the confidence interval for the difference in relapse proportions did not exceed 27.2% (*i.e.*, the sum of the 11.2% margin and the 16.0% expected relapse proportion). The required sample size was calculated as 80 patients. However, due to insufficient enrollment of the expected number of cases, we determined that testing for non-inferiority would not be appropriate. Therefore, analyses of endpoints were limited to summarization and estimation. Baseline characteristics data were expressed as medians and interquartile ranges (IQR) for continuous variables and numbers with percentages for discrete variables. For interval estimation such as a confidence interval (CI), an Wilson's score method was used. R version 4.4.0 (R Project for Statistical Computing, Vienna, Austria) was used for statistical analyses.

## 3. Results

### 3.1. Patients' characteristics

This study included 19 patients between October 11, 2019, and March 31, 2023, although the target enrollment was 80 patients. Among the enrolled patients, 18 patients were evaluated for DAS28-ESR at 24 weeks or study discontinuation (full analysis set [FAS]) (Figure 1).

Table 1 shows the baseline characteristics of the patients. The age of the patients was 63 years (51, 72), with 6 males (33%) and 12 females (67%). The disease duration of RA was 9 years (6, 12.3). Fifteen (83%) were RF positive, and 17 (94%) were ACPA positive. The duration of the originator IFX treatment was 6.4 years (3.4, 9.5), and the duration of maintenance of clinical remission was 83 weeks (25, 151). The baseline originator IFX dose was 4.5 mg/kg (3, 8.25), and the dosing interval was 8 weeks (8, 8.75). The methotrexate dose at baseline was 8 mg/week (8, 10), and two patients (11%) were receiving concomitant PSL at baseline at a dose of 4 mg/day (3.5, 4.5). Before the baseline visit, prior use of other bDMARDs or JAK inhibitors was observed in two patients with etanercept, one with tocilizumab, one with abatacept, and one with tofacitinib.

### 3.2. Primary endpoint

The proportion of study subjects who experienced clinical relapse from baseline to week 24 after the start of treatment was 2 out of 18 [11.1% (95% CI: 3.1–32.8)]. One case relapsed at week 11 and the other at week 24.

### 3.3. Secondary endpoints

The proportion of study subjects who experienced clinical relapse from baseline to week 12 was 1 of 18 (5.5% [95% CI: 1.0–25.8]).

Table 2 presents the changes in the total GS and

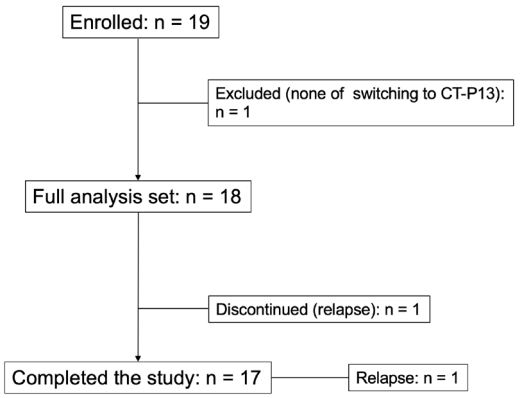


**Figure 1. Patient flow chart.**

PD scores, GLOESS, DAS28-ESR, DAS28-CRP, and HAQ-DI values from baseline to weeks 12 and 24, and the changes in vdH-mTSS from baseline to week 24. Figure 2 illustrates the distribution of the actual values for each outcome measure. Patients who discontinued treatment due to relapse had increased total GS and PD scores, GLOESS, DAS28-ESR, DAS28-CRP, and HAQ-DI values. However, no changes in these values were observed overall from baseline to weeks 12 and 24. The PD scores at weeks 12 and 24 remained at 0, indicating PD remission in the MSUS assessment. The clinical assessments at weeks 12 and 24 revealed sustained remission.

Figure 3 shows the changes in multiple cytokine arrays and ELISA from baseline to weeks 12 and 24 and stop visit and Supplementary Table S1 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=268*) shows cytokine/chemokine levels at the baseline. All the cytokines/chemokines showed no apparent changes from baseline to weeks 12 and 24. However, in a single patient in whom the study was discontinued because of relapse, serum levels of G-CSF, IL-6, PDGF-AA, MCP-1, VEGF-A, and IL-27 increased, whereas serum levels of eotaxin, IL-5, and MDC decreased. In addition, RF, ACPA, and MMP-3 levels did not change from baseline to weeks 12 and 24 (data not shown).

**Table 1. Baseline characteristics**

| | *n* = 18 |
|---|---|
| Age, years | 63 (51, 72) |
| Female | 12 (67) |
| Height, cm | 162 (154, 167) |
| Weight, kg | 54 (46, 63) |
| Disease Duration, year | 9.0 (0.0, 6.5) |
| Rheumatoid factor-positive | 15 (83) |
| Anti-cyclic citrullinated peptide antibody-positive | 17 (94) |
| Duration of remission, week | 83 (25, 151) |
| Duration of Infliximab use, year | 6.4 (3.4, 9.5) |
| Infliximab dose, mg/kg | 4.5 (3.0, 8.25) |
| Infliximab dose interval, week | 8 (8, 8.75) |
| History of infusion reaction to Infliximab | 0 (0) |
| Smoking history | 9 (50) |
| Current smoker | 2 (11) |
| Former smoker | 7 (39) |
| Pretreatment for rheumatoid arthritis | |
| Biologics agents | |
| Etanercept | 2 (11) |
| Tocilizumab | 1 (5.6) |
| Abatacept | 1 (5.6) |
| JAK inhibitors | |
| Tofactinib | 1 (5.6) |
| Concomitant medications | |
| Methotrexate | 18 (100) |
| Methotrexate dose, mg/week | 8 (8.0, 10.0) |
| Prednisolone | 2 (11) |
| Prednisolone dose, mg/day | 4 (3.5, 4.5) |
| Iguratimod | 3 (16.7) |
| Tacrolimus | 1 (5.6) |
| Tacrolimus, Iguratimod, and Salazosulfapyridine | 1 (5.6) |

Data are shown as *n* (%) or median (IQR). IQR, interquartile range; JAK, Janus kinase.

### 3.4. Safety

In the safety analysis set (18 patients), three adverse events (eczema, dry dermatitis, and COVID-19) occurred from the start of treatment to week 24. Serious adverse events were not observed. All non-serious adverse events were grade 2 and moderate in severity (requiring minimal/local/non-invasive treatment for adverse events). No adverse events led to study discontinuation.

## 4. Discussion

In this study, most patients who underwent treatment with originator IFX in clinical remission could safely switch to biosimilar IFX, CT-P13, without increased relapse risk. In addition, few changes were observed in MSUS scores, levels of cytokines/chemokines, as well as clinical indices, including DAS28-ESR and DAS28-CRP, among the patients who completed the 24-week

**Table 2. Assessment of efficacy**

| Items | Median (IQR) |
|---|---|
| **Total GS score** | |
| changes 0-12 weeks (*n* = 17) | 0 (0, 0) |
| changes 0-24 weeks (*n* = 17) | 0 (-1, 0) |
| changes 0 week-stop (*n* = 1) | 3 |
| **Total PD score** | |
| changes 0-12 weeks (*n* = 17) | 0 (0, 0) |
| changes 0-24 weeks (*n* = 17) | 0 (0, 0) |
| changes 0 week-stop (*n* = 1) | 2 |
| **GLOESS** | |
| changes 0-12 weeks (*n* = 17) | 0 (0, 0) |
| changes 0-24 weeks (*n* = 17) | 0 (-1, 0) |
| changes 0 week-stop (*n* = 1) | 3 |
| **DAS28-ESR** | |
| changes 0-12 weeks (*n* = 17) | -0.06 (-0.22, 0.36) |
| changes 0-24 weeks (*n* = 17) | 0.15 (-0.08, 0.81) |
| changes 0 week-stop (*n* = 1) | 2.6 |
| **DAS28-CRP** | |
| changes 0-12 weeks (*n* = 16) | 0.08 (-0.01, 0.29) |
| changes 0-24 weeks (*n* = 17) | 0.13 (-0.05, 0.54) |
| changes 0 week-stop (*n* = 1) | 3.4 |
| **HAQ-DI** | |
| changes 0-12 weeks (*n* = 17) | 0 (0, 0) |
| changes 0-24 weeks (*n* = 17) | 0 (0, 0) |
| changes 0 week-stop (*n* = 1) | 0 |
| **vdH-mTSS** | |
| changes 0-24 weeks (*n* = 17) | 0 (0, 0) |

CRP, C-reactive protein; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; GLOESS, Global Outcome Measures in Rheumatology European Alliance of Associations for Rheumatology Synovitis Score; GS, gray scale; HAQ-DI, Health Assessment Questionnaire-Disability Index; IQR, Interquantile range, vdH-mTSS, van der Heijde-modified total Sharp score; PD, power Doppler.

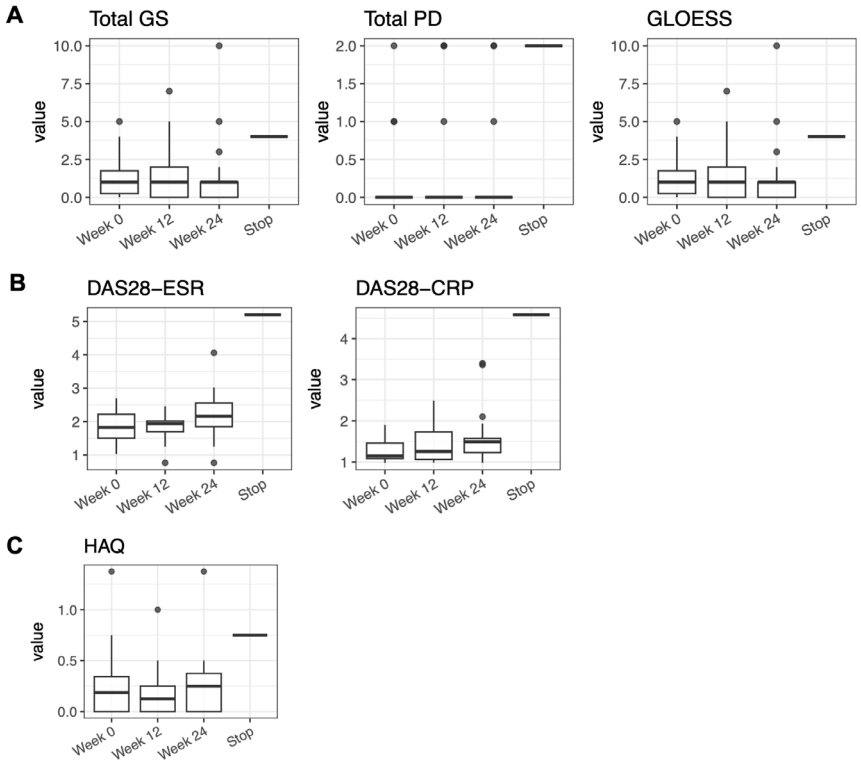


**Figure 2. Changes in MSUS scores, clinical disease activity, and HAQ-DI during the study period.** A. MSUS scores, B. clinical disease indices, and C. HAQ-DI. Horizontal bar: median; boxes: 25th and 75th percentiles; bars: 5th and 95th percentiles. CRP, C-reactive protein; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; GLOESS, Global OMERACT-EULAR Synovitis Score; GS, grayscale; HAQ-DI, Health Assessment Questionnaire-Disability Index; MSUS, musculoskeletal ultrasound; PD, power Doppler.

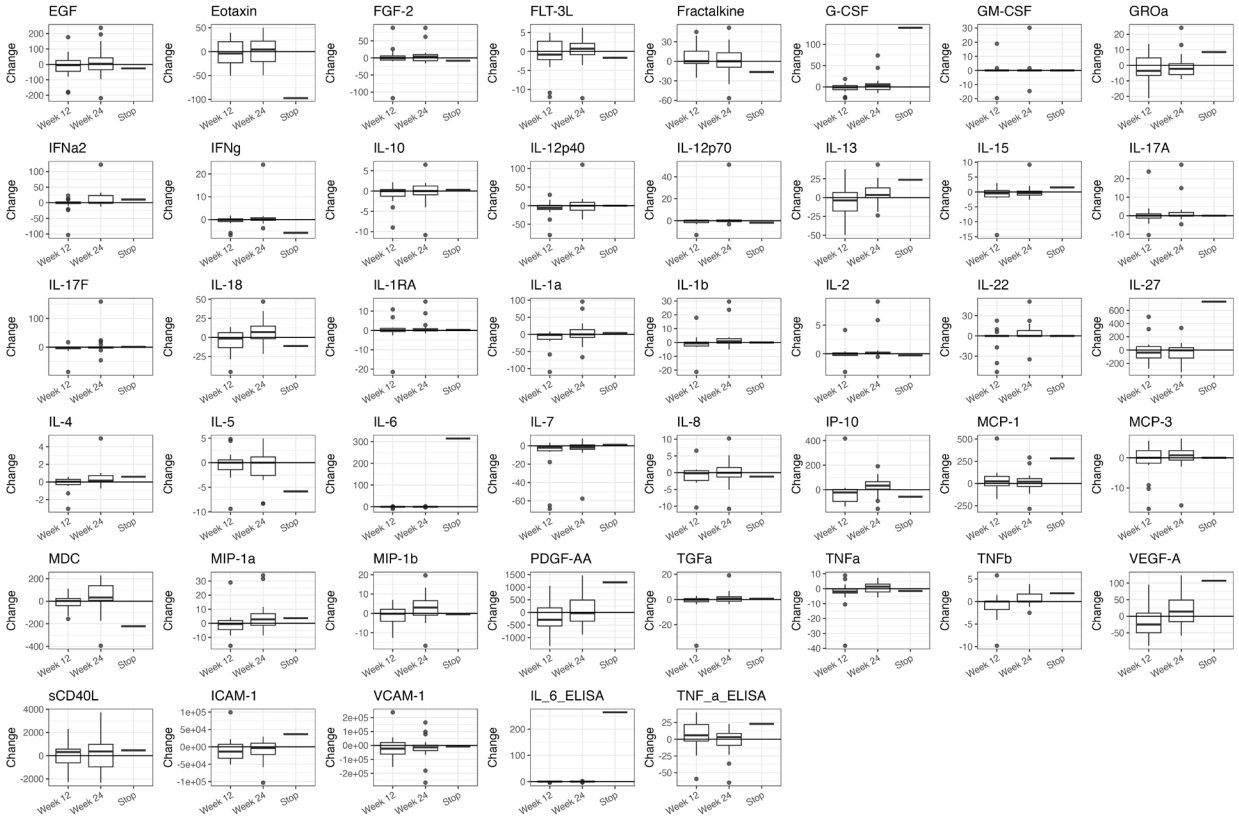


**Figure 3. Changes in multiple cytokine and chemokine levels during the study period.** Horizontal bar: median; boxes: 25th and 75th percentiles; bars: 5th and 95th percentiles.

study duration.

Introducing biologics into clinical practice has dramatically improved the management of various immune-mediated inflammatory diseases, including RA (*28*). However, the high cost of currently available biologics limits access to treatment for patients with RA (*29,30*). Biosimilars provide potential cost savings and health benefits, playing a crucial role in the treatment of rheumatic diseases (*8,30,31*). The price of a pharmaceutical product is a key factor in drug selection, and the cost reduction for CT-P13 was 38% (in terms of the average NHI price as of December 2024) compared with the originator IFX in Japan. Therefore, the Japanese government has promoted using biosimilars to reduce healthcare costs. However, some physicians are cautious about their clinical use, questioning their efficacy and safety. Additionally, there are concerns regarding the nocebo effect of switching to biosimilars (*32,33*).

The efficacy and safety equivalence of biosimilar IFX, including CT-P13, to originator IFX in patients with RA have been demonstrated (*7,34,35*). In addition, several studies have shown the efficacy and safety of switching from originator IFX to biosimilar IFX (*8,9,30,36*). One randomized control trial reported that patients with several inflammatory diseases, including RA, after switching from originator IFX to CT-P13, were not inferior to continued treatment with originator IFX (*8*). In a Danish registry, clinical relapse ($\Delta$DAS28 $\geq$ 1.2) was observed in 10 of 346 patients with RA and psoriatic arthritis within 3 months after switching from originator IFX to CT-P13 (*36*). Similarly, in this study, clinical relapse following the switch to CT-P13 was infrequent, with only one of 18 patients experiencing relapse at week 12 and another 1 of 18 at week 24.

The strength of this study is its prospective evaluation of therapeutic efficacy using not only clinical disease activity indices but also MSUS to accurately and objectively evaluate disease activity at the joint level in a patient series. Actually, the results of this study demonstrated that in non-clinical relapsed cases, there were no changes in imaging evaluations with MSUS as well as in clinical disease activity indices. In addition, the results showed no alterations in functional assessments using HAQ-DI and multiple serum biomarker levels, confirming the absence of disease progression in RA from multiple perspectives.

In the pathophysiology of RA, it has been elucidated that intracellular signaling activity mediated by inflammatory cytokines, such as TNF-α and IL-6, plays a critical role in developing synovitis and the progression of joint destruction (*37*). In this study, we evaluated the serum levels of multiple cytokines/chemokines after switching to biosimilar IFX. Previous studies have reported that baseline multi-biomarker disease activity scores, including serum IL-6 and VEGF-A, can predict disease relapse following discontinuation of TNF inhibitors in patients with RA who have low disease activity while on TNF inhibitors (*38*). However, no study has investigated the relationship between longitudinal changes in cytokine/chemokine levels and clinical relapse. In this study, no changes in cytokine/chemokine levels were observed in non-clinical relapsed cases. In contrast, one relapsed case showed fluctuations in multiple cytokines, including IL-6, at the time of relapse. Nevertheless, because this observation was based on a single case, further studies are warranted to elucidate the relationship between cytokine dynamics and disease relapse.

This study had some limitations. First, the sample size was small. Only 18 patients were evaluated, although 80 patients were expected to be enrolled. Thus, the initially planned test of non-inferiority to originator IFX could not be evaluated, and analyses of primary endpoint were limited to summarization and estimation. In addition, the analysis of the other endpoints primarily consisted of summarization. Second, the present study only covered a period of 24 weeks, indicating the need for future studies to assess the long-term outcomes. Third, immunogenicity such as anti-drug antibodies and neutralizing antibodies was not assessed; thus, their relationship with relapse was not investigated. Fourth, another aim of this study was to identify the predictive factors for clinical relapse after switching from originator IFX to CT-P13. However, due to the limited number of relapse cases, it was not feasible to conduct an analysis to identify the predictive factors. Despite these limitations, this study represents a prospective evaluation of therapeutic efficacy utilizing not only clinical disease activity indices but also MSUS and several biomarkers; consequently, these results possess considerable clinical value.

In conclusion, this study revealed that although the results were limited to estimations due to the small number of cases, a large proportion of Japanese patients with RA who achieved clinical remission were able to maintain non-clinical relapse after switching from originator infliximab to biosimilar infliximab. This study highlighted the potential for cost-effective biosimilars to maintain remission in patients with RA, suggesting significant implications for reducing treatment costs and improving accessibility.

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