Global Health & Medicine. 2025; 7(4):334-339.
DOI: 10.35772/ghm.2025.01054

CORRESPONDENCE

Discontinuation of biosimilar infliximab in Japanese patients with rheumatoid arthritis achieving sustained clinical remission or low disease activity during the IFX-SIRIUS STUDY I (the IFX-SIRIUS STUDY II): A clinical, ultrasound, and biomarker-based effectiveness after discontinuation and reinitiation of biosimilar infliximab

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Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting synovial joints. Biosimilar disease-modifying anti-rheumatic drugs offer cost-effective alternatives to originator biologics for RA treatment but remain expensive for long-term use. This prospective study investigated the clinical benefit of discontinuing CT-P13, a biosimilar of infliximab, in RA patients maintaining clinical remission or low disease activity. Five patients were enrolled from the IFX-SIRIUS STUDY I. CT-P13 was discontinued for 48 weeks, with evaluation using clinical indices, musculoskeletal ultrasound (MSUS), and serum biomarkers. Two patients experienced clinical relapse at weeks 5 and 36. The patient who relapsed at week 36 was re-administered CT-P13 and showed improved clinical outcomes without adverse events. Patients with non-clinical relapse showed no changes in disease activity scores or MSUS scores, with no notable alterations in serum cytokine levels. Over 50% of the patients maintained non-clinical relapse after CT-P13 discontinuation, and relapsed patients improved after re-administration without adverse events. This study was registered in the Japan Registry of Clinical Trials (*https://jrct.mhlw.go.jp*) on April 20, 2020, as jRCTs071200007.

Keywords: rheumatoid arthritis, biosimilar, infliximab CT-P13, musculoskeletal ultrasound, biomarker, drug discontinuation

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects the synovial joints (*1*). The uncontrolled disease activity of RA may lead to joint destruction and deformity, thus impairing patients' quality of life. Therefore, tight control of disease activity using a treat-to-target strategy is recommended to prevent joint destruction (*2*). Advancements in RA treatment, including the use of biological originator disease-modifying anti-rheumatic drugs (bDMARDs) and biosimilar DMARDs (bsDMARDs), have improved clinical outcomes, enabling the achievement of low disease activity or clinical remission in patients with RA.

We conducted the IFX-SIRIUS STUDY I (jRCTs071190030) to evaluate the efficacy and safety of switching from originator infliximab (IFX) to CT-P13, a biosimilar of originator IFX in patients with RA achieving clinical remission (*3*). The study showed that clinical relapse following the switch to CT-P13 was infrequent, with only two of 18 patients experiencing relapse within 24 weeks. Patients who completed the 24-week study period showed minimal alterations in musculoskeletal ultrasound (MSUS) scores, cytokine/

chemokine levels, and clinical indices. Switching from bDMARDs to bsDMARDs is expected to reduce patients' economic burden and improve medical insurance finances. However, continuing bsDMARDs remains costly. Notably, several reports have shown the clinical benefits of discontinuing bDMARD in patients with RA (*4-6*). Thus, we expected that patients with RA would be able to maintain good outcomes after discontinuing CT-P13. However, there is no evidence of an optimal approach for discontinuing bsDMARDs such as CT-P13.

Hence, in this study, we aimed to investigate the clinical benefit of discontinuing CT-P13 in patients with RA, maintaining clinical remission or low disease activity by treating with CT-P13 during the IFX-SIRIUS STUDY I. In addition, we aimed to evaluate the disease activity using clinical disease activity indices and MSUS to accurately assess inflammation at the joint level, continuing from the IFX-SIRIUS STUDY I and evaluate the effectiveness and safety of CT-P13 retreatment in patients with RA who experienced clinical relapse.

2. Study design

This prospective, open-label, interventional, single-arm clinical trial was conducted at 19 centers across Japan (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=105*). The study was registered in the Japan Registry of Clinical Trials as jRCTs071200007, and approved by the certified review board of Nagasaki University (CRB20-003). Written informed consent was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki (*7*), 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 study protocol has been previously published (*8*), where the detailed methodology is described. Accordingly, only the principal methods are outlined in this section.

2.1. Participants

The inclusion criteria were: *i*) treatment with CT-P13 and non-clinical relapse during IFX-SIRIUS STUDY I, and *ii*) ability to give written informed consent and comply with study requirements. Key exclusion criteria included: *i*) history of infusion reaction to CT-P13 requiring medication, and *ii*) glucocorticoid or conventional synthetic DMARD dose changes after IFX-SIRIUS STUDY I.

2.2. Intervention

The patients discontinued intravenous CT-P13 throughout the study period. In cases of clinical relapse, CT-P13 was re-administered at 3 mg/kg at 0, 2, and 6 weeks, followed by maintenance doses every 8 weeks. All patients continued the same doses of methotrexate and oral glucocorticoids received before CT-P13 discontinuation. Clinical relapse was defined as: *i*) ΔDisease Activity Score-28 (DAS28)-erythrocyte sedimentation rate (ESR) ≥ 1.2 or DAS28-ESR ≥ 3.2, and *ii*) increased DAS28-ESR due to RA disease activity rather than other factors.

2.3. Outcome measurements

The study visits were conducted at baseline and 12, 24, 36, and 48 weeks after CT-P13 discontinuation (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=105*). Clinical disease activity was evaluated using DAS28-ESR and DAS28-C reactive protein (CRP) values. Patient functional assessment was evaluated using the Health Assessment Questionnaire-Disability Index (HAQ-DI). MSUS imaging was performed at baseline, week 48, and clinical relapse using a multifrequency linear transducer (12–24 MHz). Joint synovitis was assessed at 22 joints using grayscale (GS) and power Doppler (PD) scores (0–3 scale). We also assessed GLOESS. X-ray images of bilateral hands and feet were evaluated using the van der Heijde-modified total Sharp score (vdH-mTSS) method. Serum concentrations of rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (ACPA), and matrix metalloproteinase-3 (MMP-3) were measured using standard assays. Multiplex cytokine/chemokine bead assays were performed using MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel to measure 41 cytokines and chemokines. Serum interleukin-6 and tumor necrosis factor-α levels were measured using specific ELISA kits.

2.4. Study endpoints

The primary endpoint was the proportion of patients experiencing clinical relapse between baseline and week 48. Secondary endpoints included changes in total PD and GS scores, GLOESS, DAS28 values, vdH-mTSS, HAQ-DI scores, and serum biomarker levels from baseline to various time points. Safety endpoint was the occurrence of adverse events.

2.5. Statistical analysis

The primary analysis was planned to estimate the 95% confidence interval of the proportion of patients with clinical relapse using Wilson's score interval (*9*). However, statistical estimations were excluded due to small sample size (five patients), and individual data points were presented instead. The graphs were created using GraphPad Prism (version 9.5.1; GraphPad Software, La Jolla, CA).

3. Patients' characteristics

In IFX-SIRUS STUDY I, 16 patients completed the study period without clinical relapse. In contrast, five patients were included in this study between April 20, 2020 and December 31, 2023. These five cases were enrolled from three participating institutions. Supplemental Table S2 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=105*) shows the baseline patient characteristics.

The patients (three females and two males) were 74, 73, 63, 51, and 49 years old. All patients tested positive for RF and ACPA. The dosage and interval of CT-P13 were 6 mg/kg every 8 weeks in 2 cases and 3 mg/kg every 8, 12, or 14 weeks in the other cases. The methotrexate dose at baseline was 6 mg/week in one case, 8 mg/week in three cases, and 10 mg/week in one case. One patient received prednisolone at a dose of 5 mg/day. No case involved the concomitant use of csDMARDs other than methotrexate. None of the patients had a history of treatment with bDMARDs, except for the originator IFX and CT-P13. One patient had a history of treatment with the JAK inhibitor, tofacitinib.

4. The endpoints

The primary endpoints showed that of the five patients in the study, two experienced clinical relapses by week 48. One patient (Case 4) relapsed at week 5, leading to discontinuation of the study, while another patient (Case 5) relapsed at week 36 and was subsequently re-administered CT-P13.

Table 1 presents the longitudinal clinical and laboratory data, including DAS28-ESR, DAS28-CRP, HAQ-DI, the total GS and PD scores, GLOESS, and vdH-mTSS during the study period. Figure 1 illustrates the actual values of DAS28-ESR for each participant. Patients who achieved non-clinical relapse showed no changes in DAS28 values and MSUS scores during the study period. In one case of relapse (Case 4, relapse at week 5), DAS28-ESR increased from 1.25 at baseline to 4.35 at relapse, and GLOESS increased from 3 at baseline to 8 at relapse. In the other case (Case 5, relapse at week 36), DAS28-ESR increased from 2.85 at week 24 to 4.14 at relapse and improved to 2.38 at week 48 after re-administering CT-P13. In addition, the HAQ-DI value improved from 0.5 at relapse to 0.125 at week 48 after the re-administration of CT-P13. However, Case 5 showed almost no change in MSUS score at relapse. In addition, no changes were observed in vdH-mTSS during the study period. Supplemental Table S3 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=106*) shows the levels of multiple cytokine arrays and ELISA during the study period. The results revealed that neither clinical relapse nor non-relapse cases exhibited notable alterations in any cytokine level. During the study period, no adverse events occurred in the safety analysis.

In this study, of the patients with RA who maintained clinical remission or low disease activity during IFX-SIRIUS STUDY I, we observed non-clinical relapses in three cases, while two patients experienced clinical relapse after discontinuing CT-P13. Of the two patients who experienced a relapse, the one who was re-administered CT-P13 had improved clinical disease activity indices and patient-reported outcomes, including DAS28-ESR, DAS28-CRP, and HAQ-DI values without any adverse events after re-administration of CT-P13.

The introduction of bDMARDs in clinical practice has dramatically improved the outcomes of patients with RA. However, the currently available bDMARDs are expensive, and this has led to restricted treatment access in patients with RA. Switching from originator infliximab to CT-P13 plays an important role in cost savings and health gains for patients with RA. However, the long-term continuation of CT-P13 remains costly.

Notably, several studies have demonstrated the clinical impact of discontinuing bDMARDs in patients with RA. In particular, the majority of these studies have focused on TNF inhibitors (*4,5,10-15*). The previous prospective studies have shown that among patients with RA with remission or low disease activity, the proportion of those who maintained non-clinical relapse 1 year after discontinuing TNF inhibitors varied widely, ranging from as low as 13% (*12*) to as high as 62% (*5*). In this study, although the number of cases was limited to five, over 50% (three cases) showed non-clinical relapse during the 52-week study period. In addition, among the two relapsed cases, one patient who was re-administered CT-P13 showed improvement in disease activity without adverse events, including infusion reactions.

The strength of this study was that it prospectively evaluated the therapeutic effectiveness of CT-P13 using clinical disease activity indices and standardized MSUS findings, which accurately and objectively evaluated disease activity at the joint level and the serum levels of multiple biomarkers, such as cytokines and chemokines.

Residual synovitis, such as the PD score detected using MSUS, is a risk factor for relapse in patients with RA who maintain clinical remission (*16*). In addition, some reports have suggested that a positive PD score in patients with RA with clinical remission is associated with an increased risk of relapse following discontinuation of bDMARDs (*17,18*). In this study, the total PD score at the time of CT-P13 discontinuation was zero in all cases, indicating that only the PD score might be insufficient to predict relapse. However, the PD score remained zero throughout the study period after CT-P13 discontinuation in non-clinical relapsed cases, indicating non-clinical relapse and the absence of synovitis progression, as evaluated by MSUS during the study period.

The association between serum cytokine levels

Table 1. Longitudinal clinical, laboratory data, the musculoskeletal ultrasound score and vdH-mTSS

Subject numbers	Visit	DAS28-ESR	DAS28-CRP	HAQ-DI	Patient global VAS	SJC (28 joints)	TJC (28 joints)	ESR (mm/H)	CRP (mg/dL)	Total GS score	Total PD score	GLOESS	vdH-mTSS
Case 1	Baseline	2.16	1.49	0.375	0	0	0	22	0.332	10	0	10	48.5
	Week 12	2.84	2.33	0.375	5	0	0	52	3.6				
	Week 24	2.48	1.93	0.25	1	0	0	34	1.34				
	Week 36	2.43	1.7	0.25	0	0	0	32	0.683				
	Week 48	2.64	1.89	0.375	8	0	0	37	0.878	9	0	9	49
Case 2	Baseline	0.77	0.98	0	0	0	0	3	0.005	0	0	0	12
	Week 12	1.25	0.99	0	0	0	0	6	0.008				
	Week 24	1.13	0.99	0	0	0	0	5	0.009				
	Week 36	0.97	0.99	0	0	0	0	4	0.009				
	Week 48	1.13	1	0	0	0	0	5	0.011	0	0	0	12
Case 3	Baseline	2.56	1.54	0.375	7	2	0	19	0.028	1	0	1	35
	Week 12	2.23	1.3	0.25	5	0	0	22	0.114				
	Week 24	2.22	1.09	0.375	0	0	0	24	0.042				
	Week 36	2.37	1.25	0.375	3	0	0	28	0.097				
	Week 48	2.44	1.33	0.125	0	1	0	22	0.027	1	0	1	35
Case 4	Baseline	1.25	1.34	0	0	0	0	6	0.19	3	0	3	11.5
	Week 5 (relapse)	4.35	3.84	0.25	20	3	5	28	0.988	7	2	8	N/A
Case 5	Baseline	1.68	1.25	0.25	10	0	0	9	0.05	0	0	0	82
	Week 12	1.85	1.27	0	0	0	0	14	0.135				
	Week 24	2.85	2.63	0.25	10	0	5	8	0.116				
	Week 36 (relapse)	4.14	3.62	0.5	20	3	8	13	0.14	1	0	1	N/A
	Week 48	2.38	1.8	0.125	10	0	1	11	0.046	0	0	0	82

CRP, C-reactive protein; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; GLOESS, Global OMERACT-EULAR Synovitis Score; GS, gray scale; HAQ-DI, Health Assessment Questionnaire-Disability Index; N/A, not available; PD, power Doppler; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale; vdH-mTSS, van der Heijde-modified total Sharp score

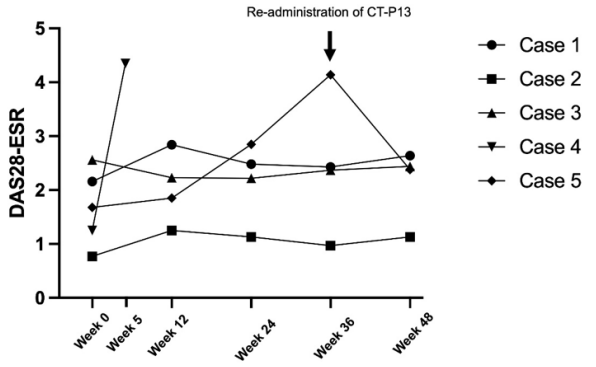

Figure 1. Longitudinal changes in the DAS28-ESR for each participant.

and relapse following discontinuation of bDMARDs in patients with RA has been investigated in several studies. One study demonstrated that certain serum cytokines, including IL-34, CCL1, IL-1β, IL-2, and IL-19, can predict relapse in patients with RA after discontinuation of bDMARDs (*19*). In addition, another study has revealed that a combination of 12 biomarkers, including VCAM-1, EGF, VEGF, and IL-6, may predict relapse after discontinuation of bDMARDs (*20*). In this study, no noticeable changes in serum cytokine levels were observed during the study period. Given the limited number of cases, further research is required to elucidate the relationship between relapse after CT-P13 discontinuation and serum cytokine levels.

This study had some limitations. First, the sample size was small; only five patients were evaluated. Thus, the planned analyses involving statistical estimation could not be evaluated. Second, we also aimed to identify the predictive factors for clinical relapse after discontinuing CT-P13. However, with only two relapse cases, it was not possible to explore predictive factors following the discontinuation of CT-P13. To overcome these limitations, it is essential to enroll and analyze a larger number of cases. However, this study provides a prospective evaluation of therapeutic change by incorporating clinical disease activity indices, MSUS, and multiple biomarkers. As a result, the findings offer substantial clinical value.

In conclusion, we revealed that over 50% of patients with RA who achieved clinical remission or low disease activity maintained non-clinical relapse after discontinuing CT-P13. In addition, one patient who experienced relapse showed improved disease activity without any adverse events after the re-administration of CT-P13. Future research should focus on investigating the long-term effects and predicting relapse after discontinuation of biosimilars using a larger sample size.

Acknowledgements

We thank Nobutaka Eiraku (Eiraku Internal Medicine Clinic), Tadashi Okano (Osaka Metropolitan University Graduate School of Medicine), Tamami Yoshitama (Yoshitama Clinic for Rheumatic Diseases), Kiyoshi Migita, and Shuzo Sato (Fukushima Medical University School of Medicine), Shin-Ichiro Kagami (Asahi General Hospital), Takuya Nakazawa (Chiba-East Hospital), Seiji Yoshizawa (Hamanomachi Hospital), Takahisa Suzuki (Japanese Red Cross Nagasaki Genbaku Hospital), Etsuo Chosa (University of Miyazaki Hospital), Toshihiko Hidaka (Miyazaki Zenjinkai Hospital), Masako Furuyama (Nagasaki Kita Hospital), Toru Takeuchi (Osaka Medical and Pharmaceutical University Hospital), Akira Sagawa (Sagawa Akira Rheumatology Clinic), Ikuko Onishi (Utazu Hospital), and Kazuyoshi Saito (Tobata General Hospital), all of which are investigators of joint research institutions. We thank our colleagues and staff at the Department of Immunology and Rheumatology, Nagasaki University Hospital for their support.

Funding: This study was funded by Celltrion Healthcare Co., Ltd. (Incheon, South Korea).

Conflict of Interest: Atsushi Kawakami received research funding from AYUMI Pharmaceutical Co., Celltrion Healthcare Japan K.K., Gilead Sciences Inc., KIYAN PHARMA Co. Ltd., Janssen Pharmaceutical K.K., ONO Pharmaceutical Co., Asahi Kasei Pharma Corporation, Taisho Pharmaceutical Co. Ltd., Teijin Pharma Co., Chugai Pharmaceutical Co., Kyowa Kirin Co., Boehringer Ingelheim Japan, Abbvie GK, Eli Lilly Japan, Daiichi Sankyo Co., Mitsubishi Tanabe Pharma Co., Bristol-Myers Squibb, and Eisai Co. The other authors have no conflicts of interest to declare.

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Received May 16, 2025; Revised July 24, 2025; Accepted July 27, 2025.

Released online in J-STAGE as advance publication July 31, 2025.

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