Original Article

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Efficacy of etanercept biosimilar switching from etanercept reference product, using ultrasound and clinical data in outcomes of real world therapy (ESCORT-NGSK Study)

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SUMMARY: This study aimed to investigate in detail the efficacy of switching from etanercept reference product (RP) to etanercept biosimilar in patients with rheumatoid arthritis (RA) under real-world clinical conditions using clinical indices and musculoskeletal ultrasound (MSUS). This interventional, multicenter, open-label, single-arm clinical trial involved 24- or 52-week follow-up. This study enrolled patients with RA who had been treated with etanercept-RP for ≥ 24 weeks, achieved clinical low disease activity (LDA) or remission, and switched from etanercept-RP to etanercept biosimilar. This study included 20 patients. Of the 17 patients, 16 (94.1%; 95% confidence interval [CI]: 71.3–99.9) remained in LDA/remission on DAS28-ESR at 24 weeks. The dose of 50 mg/week was reduced to 25 mg/week at 24 weeks, and LDA/remission was sustained until 52 weeks in 9 (81.8%, 95% CI: 48.2–97.7] of 11 participants. DAS28-ESR, DAS28-CRP, SDAI, and CDAI scores showed no apparent worsening. The median total PD score remained 0. The switch from etanercept-RP to etanercept biosimilar and subsequent dose reduction demonstrated favorable outcomes, including MSUS evaluation.

Keywords: Rheumatoid arthritis (RA), etanercept, biosimilar, musculoskeletal ultrasound (MSUS), biomarkers

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease caused by multiple genetic and environmental factors that triggers autoimmune responses, inducing chronic synovitis in multiple joints, progressive destructive arthritis, and physical dysfunction (*1*). Therefore, the primary treatment goal is to achieve remission through tight control using a treat-to-target strategy (*2*). The advent of biological disease-modifying antirheumatic drugs (bDMARDs) has significantly increased clinical remission rates and expanded the treatment options. However, the high cost of bDMARDs imposes a significant economic burden, making their introduction and continued treatment difficult for some patients. Hence, biosimilars have emerged as a treatment option for RA, anticipated to alleviate patients' economic burden and support healthcare insurance sustainability. In Japan, etanercept biosimilar 1 (brand name Etanercept BS "MA") gained marketing approval in January 2018, matching the indication of etanercept-RP (brand name Enbrel). Etanercept biosimilar 1 is a biologic similar to etanercept-RP, and its equivalence in quality, efficacy, and safety at the time of approval was verified and proven in clinical trials compared to etanercept-RP (*3*). Additionally, the aforementioned studies assessed the efficacy of long-term etanercept biosimilar 1 administration (*3,4*). However, the efficacy of switching

from etanercept-RP to etanercept biosimilar 1 remains unconfirmed under real-world clinical conditions, and no report has evaluated the efficacy of switching from etanercept-RP to etanercept biosimilar in detail using musculoskeletal ultrasound (MSUS) or multiple serum biomarkers.

MSUS, which is non-invasive, objective, inexpensive, and repeatable, surpasses clinical disease activity assessment because it depicts synovial inflammation with high sensitivity (*5,6*). In addition, it is a valuable imaging tool for monitoring the treatment. MSUS reveals subclinical synovitis, a significant finding predictive of joint destruction and relapse even in cases of clinical remission (*7,8*). Therefore, it is important to accurately assess disease activity at the joint level using MSUS and not just clinical disease activity indices that include subjective factors. A multicenter study that prospectively assessed RA activity using MSUS is rare globally. This multicenter study conducted a high-level standardized MSUS assessment and revealed results with clinical value.

A major concern for clinicians is how to continue treatment of patients who achieved low disease activity (LDA)/remission through bDMARDs. The PRESERVE study revealed that reducing the dose of etanercept-RP from 50 mg/week to 25mg/week is beneficial in maintaining LDA/remission in patients who have sustained these levels (*9*). However, the association of reducing the dose of an etanercept biosimilar with maintaining LDA/remission in patients with a good course of treatment using the biosimilar remains unknown.

The present study assessed changes in disease activity after switching from etanercept-RP to etanercept biosimilar 1 and the subsequent dose reduction of etanercept biosimilar 1 more accurately and objectively, using both MSUS and clinical disease activity indicators.

2. Materials and Methods

2.1. Patients

This prospective, open-label, interventional single-arm clinical trial was conducted at the following seven centers: Nagasaki University Hospital, Sasebo Chuo Hospital, Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki Medical Hospital of Rheumatology, Saga University Hospital, Miyazaki-Zenjinkai Hospital, and Kumamoto Shinto General Hospital.

Inclusion criteria were (1) patients aged ≥ 20 years upon obtaining informed consent, (2) patients with RA fulfilling the American College of Rheumatology (ACR)/ European Alliance of Associations for Rheumatology (EULAR) classification criteria for RA (2010) (*10*), (3) patients treated with etanercept-RP (for subcutaneous injection of 25 mg once weekly, 25 mg twice weekly, 50 mg once weekly, or 50 mg once biweekly) for ≥ 24 weeks and who had been in LDA/remission with no change in etanercept-RP dosage for at least 24 weeks before obtaining consent, and (4) patients who signed a written informed consent after receiving sufficient information.

Exclusion criteria were (1) patients currently receiving oral prednisolone of > 7.5 mg/day upon case enrollment, (2) patients with etanercept biosimilar 1 contraindication, (3) patients who have previously used etanercept biosimilar, (4) patients under treatment with biological agents and JAK inhibitors for RA, except for denosumab, (5) patients whose prednisolone or antirheumatic drug usage and dosage were changed within 4 weeks before case enrollment, (6) patients treated with prohibited drugs or prohibited therapies within 4 weeks before case enrollment, (7) women who are currently pregnant or will not be compliant with a medically approved contraceptive regimen during the study period and lactating women, and (8) patients who were judged unsuitable for this study by the investigator.

This study was approved by (CRB) of Nagasaki University (CRB approval number: CRB7180001). This study was registered in the Japan Registry of Clinical Trials (https://jrct.niph.go.jp) as jRCTs071190046. The study was conducted in accordance with the principles of the Declaration of Helsinki (*11*), the Clinical Trials Act (since February 2019), the Act on the Protection of Personal Information and related regulatory notifications, and this clinical study protocol.

2.2. Intervention

Patients with RA receiving etanercept-RP (subcutaneous injection of 25 mg once weekly, 25 mg twice weekly, 50 mg once weekly, or 50 mg once biweekly) for > 24 weeks and persistent LDA/remission were switched from etanercept-RP to the same dose of etanercept biosimilar 1. Additionally, patients receiving etanercept biosimilar 1 at 50 mg weekly received a reduced dose of 25 mg/ week starting at 24 weeks to investigate the persistence of LDA/remission until 52 weeks. All patients needed to maintain the same csDMARDs and oral corticosteroid doses throughout the study period, as they had been taking before the study. The following treatments were prohibited during the study period: bDMARD or JAK inhibitor, concomitant immunosuppressants (azathioprine, cyclophosphamide, and cyclosporine), oral corticosteroid equivalent to > 7.5 mg/day of prednisolone, and intra-articular corticosteroid injections.

2.3. Outcome measurements

The study visits took place at baseline and after 12, 24, 36, and 52 weeks of treatment. Supplementary Figure S1 (*https://www.ddtjournal.com/action/getSupplementalData.php?ID=244*) shows the assessment schedule. Physicians were blinded to the joint assessments using MSUS.

Each attending physician evaluated clinical disease activity based on the DAS28-C-reactive protein (CRP), DAS28-erythrocyte sedimentation rate (ESR) (*12*), simplified disease activity index (SDAI) (*13*), and clinical disease activity index (CDAI) (*14*). The Health Assessment Questionnaire-Disability Index (HAQ-DI) was used to assess patients' functional status (*15*).

The participants underwent MSUS at baseline and at 12, 24, 36, and 52 weeks. A systematic multiplanar grayscale (GS) and power Doppler (PD) assessment of each patient's joint was conducted using a multifrequency linear transducer (12–24 MHz). PD was utilized based on which Doppler modality was the most sensitive on the individual machines. Doppler settings were adjusted at each hospital according to published recommendations (*16*), and standardized joint and probe positions were employed based on the guidelines published by the Japan College of Rheumatology (JCR). JCR-certified sonographers conducted MSUS assessments at each participating hospital as previously described (*17*). Articular synovitis was assessed with MSUS at dorsal views of 22 joints: bilateral wrist joints, first–fifth metacarpophalangeal (MCP) joints, first interphalangeal joints, and second–fifth proximal interphalangeal joints. Each joint was scored semi-quantitatively for GS and PD on a scale of 0–3. The sum of the GS and PD scores was considered as the total GS and PD scores, respectively. Additionally, we evaluated the Outcome Measures in Rheumatology (OMERACT)-EULAR combined with PDUS scores (*i.e.*, the combined PD score) (*18,19*). The combined PD score incorporates GS and PD scores (*18,19*). A previous investigation confirmed interobserver reliability (*20*). PD remission was defined as a PD score of 0 in 22 joints as previously described (*17,21*).

Radiographic images of the bilateral hands (posteroanterior view) and feet (anteroposterior view) were captured. 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 (*22*), including 16 areas in each hand for erosions and 15 for joint-space narrowing (*23*).

2.4. Biomarker measurements

The serum concentrations of the following biomarkers were measured. Rheumatoid factor (RF) using a latex agglutination turbidimetric immunoassay (LZ test "Eiken" RF) (Eiken Chemial, Tochigi, Japan). Anti-cyclic citrullinated peptide antibodies (anti-CCP antibodies) were detected using a chemiluminescent immunoassay (STACIA MEBLux test CCP) (Medical & Biological Laboratories Co., Ltd., Tokyo, Japan). Matrix metalloproteinase-3 (MMP-3) using a latex turbidimetric immunoassay (Panaclear MMP-3 "Latex") (Sekisui Medical Company Limited, Tokyo, Japan). Multiplex cytokine/chemokine bead assays with diluted serum supernatants and a MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel (Merck Millipore, Billerica, MA, USA)-Bio-Plex Pro Human Cytokine Assays (Bio-Rad, Hercules, CA, USA) analyzed using a Bio-Plex® MAGPIXTM Multiplex Reader (Bio-Rad) following the manufacturer's instructions.

The cytokines/chemokines that were measured with the bead panel include interleukin (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, interferon-gamma (IFN-γ), IFN-α 2, CXCL1 (growth-related oncogene), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte CSF (G-CSF), CX3CL1 (fractalkine), flt-3 ligand, fibroblast growth factor-2, eotaxin, epidermal growth factor, soluble CD40 ligand, vascular endothelial growth factor, tumor necrosis factor (TNF)-β, TNF-α, transforming growth factor-α, CCL4 (macrophage inflammatory protein [MIP]-1β), CCL3 (MIP-1α), CCL22 (macrophage-derived chemokine [MDC]), CCL7 (monocyte chemotactic protein-3), CCL2 (monocyte chemotactic protein-1), and CXCL-10 (IFN-γ-inducible protein [IP]-10). Serum IL-6 and TNF-α levels were measured using specific enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN, USA).

2.5. Study endpoints

The primary endpoint was the proportion of study participants who sustained LDA/remission at 24 weeks after switching from etanercept-RP to etanercept biosimilar 1 without clinical relapse throughout the observation period. Clinical relapse was defined as (1) two consecutive DAS28-ESR of ≥ 3.2 in specified and unspecified visits, and (2) an increase in the DAS28-ESR value caused by elevated disease activity of RA.

The secondary endpoints of this study were (1) the proportion of study participants who sustained LDA/remission at 12, 36, and 52 weeks without clinical relapse throughout the observation period; (2) changes in the total GS and PD scores and the combined PD score from baseline to 12, 24, 36, and 52 weeks; (3) changes in the DAS28-ESR and DAS28-CRP values from baseline to 12, 24, 36, and 52 weeks; and (4) changes in the SDAI and CDAI values from baseline to 12, 24, 36, and 52 weeks.

2.6. Statistical analysis method

A previous study (*4*) revealed that the proportion of participants who achieved LDA after receiving etanercept-RP, switched to etanercept biosimilar, and maintained LDA for 24 weeks was 82.5%. The present study statistically identified the sample size that would enable the estimation of the 95% confidence interval (CI) for an achievement proportion of 82.5% to be 72.5%–92.5%. The required sample size was calculated

as 55 patients. The target sample size was 62, assuming a withdrawal rate of 10%.

All data are expressed as medians and interquartile ranges (IQR) for continuous variables and numbers with percentages for discrete variables. The 95% CIs for achieving proportions were calculated using the Clopper-Pearson method. In this study, we did not perform hypothesis testing or report point estimates and 95% CIs. The widths of the 95% CIs were not adjusted for multiplicity, and the intervals may not be utilized instead of hypothesis testing. R version 4.2.2 (R Project for Statistical Computing, Vienna, Austria) was used for the statistical analyses.

3. Results

3.1. Patients

This study included only 20 patients at the end of the enrollment period. Of the enrolled patients, 17 were evaluated for DAS28-ESR and clinical relapse at 24 weeks or study discontinuation (full analysis set [FAS]). One patient discontinued the study at 24 weeks after the investigator's decision, leaving 16 patients who completed the study (Supplementary Figure S2, *https://www.ddtjournal.com/action/getSupplementalData.php?ID=244*).

Table 1 shows the baseline patient characteristics. The age of the patients was 64 years (46, 68), and 15 (88%) patients were female. The disease duration was 15 years (7, 21). RF and anti-CCP antibodies were detected in 15 (88%) and 11 (65%) patients, respectively. Other bDMARDs were administered to seven (41%) patients, including three with infliximab, one with adalimumab, two with tocilizumab, and one with abatacept (with possible duplicates among the same individuals). Concomitant medications for RA included MTX in 11 (65%) patients at a dose of 6 mg/week (6, 8). Concomitant prednisolone was administered in 2 (12%) patients at 0.88 mg/day (0.56, 1.19).

Table 1. Baseline characteristics

	n = 17
Age, years	64 (46, 68)
Sex, Female	15 (88)
Height, cm	154 (149, 157)
Weight, kg	52 (47, 56)
Disease duration, years	15 (7, 21)
Rheumatoid factor-positive	15 (88)
Anti-CCP antibody-positive	11 (65)
Duration of etanercept (Enbrel) use, year	2.1 (1.2, 5.1)
Duration of low disease activity/remission, week	67 (56, 100)
Smoking history (ever smoked)	6 (35)
Pack-year*	8 (5, 20)
Complications of osteoporosis	9 (18)
Complications of hypertension	4 (8)
Complications of dyslipidemia	3 (6)
Complications of allergic rhinitis	3 (6)
Previous use of bDMARDs	7 (41)
Infliximab†	3 (18)
Adalimumab†	1 (5.9)
Tocilizumab†	2 (12)
Abatacept†	1 (5.9)
Concomitant medications	
Methotrexate†	11 (65)
Methotrexate dose, mg/week	6 (6.0, 8.0)
Prednisolone†	2 (12)
Prednisolone dose, mg/day	0.88 (0.56, 1.19)

Data are shown as *n* (%) or median (IQR). bDMARDs: biological disease-modifying anti- rheumatic drugs, CCP: cyclic citrullinated peptide, IQR: Interquartile Range. *Missing: n = 13. †Denominator of percentage is 17 patients.

3.2. Efficacy endpoints

The primary endpoint was the proportion of study participants who sustained LDA/remission at 24 weeks after switching from etanercept-RP to etanercept biosimilar 1 without clinical relapse throughout the observation period. The results revealed 16 (94.1%) out of 17 patients (95% CI: 71.3–99.9).

The secondary endpoint was the proportion of patients who met the LDA/remission criteria at 12, 36, and 52 weeks without clinical relapse throughout the observation period. The FAS included 17 patients up to 24 weeks, and only the 50 mg/week dose group was included after 24 weeks; thus, the analysis was conducted on 11 patients after 24 weeks, excluding 1 patient whose treatment was discontinued at 24 weeks. LDA/remission was achieved in all 17 (100%) patients at 12 weeks, of which remission was achieved in 14 (82.4%) patients: 16 (94.1%) and 13 (76.5%) patients at 24 weeks, 9 (81.8%) and 8 (72.7%) patients at 36 weeks, and 10 (90.9%) and 8 (72.7%) patients at 52 weeks. Furthermore, 11 (91.7%) of 12 patients (95% CI: 61.5–99.8) successfully reduced the dose to 25 mg/week from 24 weeks after switching to the study drug in the 50 mg/week dose group. Additionally, 9 (81.8%) of 11 patients (95% CI: 48.2–97.7) reduced their dose from 24 weeks to 25 mg/week and maintained LDA/remission until week 52.

Table 2 presents the changes in the total GS and PD scores, combined PD score, DAS28-ESR, DAS28-CRP, SDAI, and CDAI values from baseline to 12, 24, 36, and 52 weeks. Figure 1 illustrates the median of the actual values for each outcome measure. No changes were observed during any period. The overall PD score remained 0, indicating PD remission in the MSUS assessment. All clinical assessments revealed sustained remission.

3.3. Exploratory endpoints

Changes in the HAQ-DI from baseline to 12, 24, 36, and 52 weeks and vdH-mTSS from baseline to 24 and 52 weeks were assessed (Table 2). The median (IQR) results for the HAQ-DI at baseline and 12, 24, 36, and 52 weeks were 0 (0, 0.5), 0 (0, 0.5), 0 (0, 0.25), 0.25 (0, 1.2), and 0

Table 2. Assessment of efficacy

	Median (IQR)
Total GS score	
changes 0-12 weeks	0 (0, 1)
changes 0-24 weeks	1 (0, 2)
changes 0-36 weeks	0 (-0.5, 1.5)
changes 0-52 weeks	1 (0.5, 2)
Total PD score	
changes 0-12 weeks	0 (0, 0)
changes 0-24 weeks	0 (0, 0)
changes 0-36 weeks	0 (0, 0)
changes 0-52 weeks	0 (0, 0)
Combined PD score	
changes 0-12 weeks	0 (0, 1)
changes 0-24 weeks	1 (0, 2)
changes 0-36 weeks	0 (-0.5, 1.5)
changes 0-52 weeks	1 (0.5, 2)
DAS28-ESR	
changes 0-12 weeks	-0.06 (-0.31, 0.05)
changes 0-24 weeks	0.03 (-0.16, 0.31)
changes 0-36 weeks	0.09 (-0.02, 0.69)
changes 0-52 weeks	0.1 (-0.1, 0.69)
DAS28-CRP	
changes 0-12 weeks	0.06 (-0.03, 0.32)
changes 0-24 weeks	0.04 (-0.05, 0.2)
changes 0-36 weeks	0.11 (-0.04, 0.61)
changes 0-52 weeks	0.14 (-0.09, 0.82)
SDAI	
changes 0-12 weeks	-0.1 (-1, 0)
changes 0-24 weeks	0 (-0.7, 0.3)
changes 0-36 weeks	0.1 (-0.3, 1.3)
changes 0-52 weeks	0 (-1.0, 2.8)
CDAI	
changes 0-12 weeks	-0.3 (-1.2, 0)
changes 0-24 weeks	-0.2 (-0.7, 0.2)
changes 0-36 weeks	-0.2 (-0.7, 1.3)
changes 0-52 weeks	0 (-1.1, 2.5)
HAQ-DI	
changes 0-12 weeks	0 (0, 1.2)
changes 0-24 weeks	0 (0, 0)
changes 0-36 weeks	0 (-0.12, 0)
changes 0-52 weeks	0 (0, 0.12)
vdH-mTSS	
changes 0-24 weeks	0 (0, 0)
changes 0-52 weeks	0 (0, 0.75)

CDAI: clinical disease activity index, CRP: C-reactive protein, DAS28: Disease Activity Score-28, ESR: erythrocyte sedimentation rate, 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, SDAI: simplified disease activity index.

(0, 1.2), respectively. The median (IQR) values for vdH-mTSS at baseline and at 24 and 52 weeks were 27 (7, 120), 27 (7, 120), and 27 (7, 94), respectively. All the assessments showed little change. Serum biomarkers were similarly evaluated at baseline and at 24, 36, and 52 weeks, with little change. RF, anti-CCP antibodies, and MMP-3 levels did not change (data not shown). Figure 2 shows the multiple cytokine array. The IL-3 and MIP-1α levels could not be measured. All cytokines/chemokines did not change before and after etanercept biosimilar 1 introduction.

3.4. Safety

The safety analysis set determined 10 adverse events (AEs) (n = 20) from the start of the study to 52 weeks. Among these, one serious AE (SAE) occurred 19 days after initiating the study drug, specifically a left renal abscess. The severity was categorized as grade 3. Consequently, the study drug was discontinued. The patient was hospitalized, underwent surgery, and recovered. The severity of other non-SAEs was categorized as grade 1: mild (no intervention required for adverse events) or grade 2: moderate (minimal/local/noninvasive treatment required). One patient discontinued the study drug because of drug eruption. This study revealed 7 patients with adverse drug reactions, including left renal abscess, acute bronchitis, nasal herpes, pneumonia, injection site reaction, drug eruption, and vomiting, from the start of the study to 52 weeks.

4. Discussion

In this study, patients with RA with disease activity that had subsided were switched from etanercept-RP to etanercept biosimilar 1, maintaining the same dose and administration frequency. The results were positive and consisted of many cases that maintained LDA/remission at 24 weeks. Furthermore, LDA/remission was maintained in approximately 80% of the patients at 52 weeks, even when the dose was reduced to 25 mg/week from week 24. Clinical assessment, MSUS score, joint vdH-mTSS score, and biomarker levels exhibited no changes.

The advent of bDMARDs has undeniably caused significant advances in the treatment of RA; however, bDMARDs are expensive, which limits access to treatment for patients with RA. Drug price is one of the most important factors for drug selection. This is a major problem in managing patients with RA, but biosimilars have demonstrated the potential to solve this problem. In phase III trials (*4,24*), switching from etanercept-RP to etanercept biosimilars was equivalent. The EULAR recommendation (*25*), ACR guidelines (*26*), and the Japan College of Rheumatology clinical practice guidelines (*27*) mention the use of biosimilars. The Japanese government is promoting the use of biosimilars because of their potential to reduce the economic burden on health care budgets. However, some physicians are cautious about the clinical use of biosimilars because of doubts regarding their efficacy and safety. Producing a generic drug with the same molecular structure as that

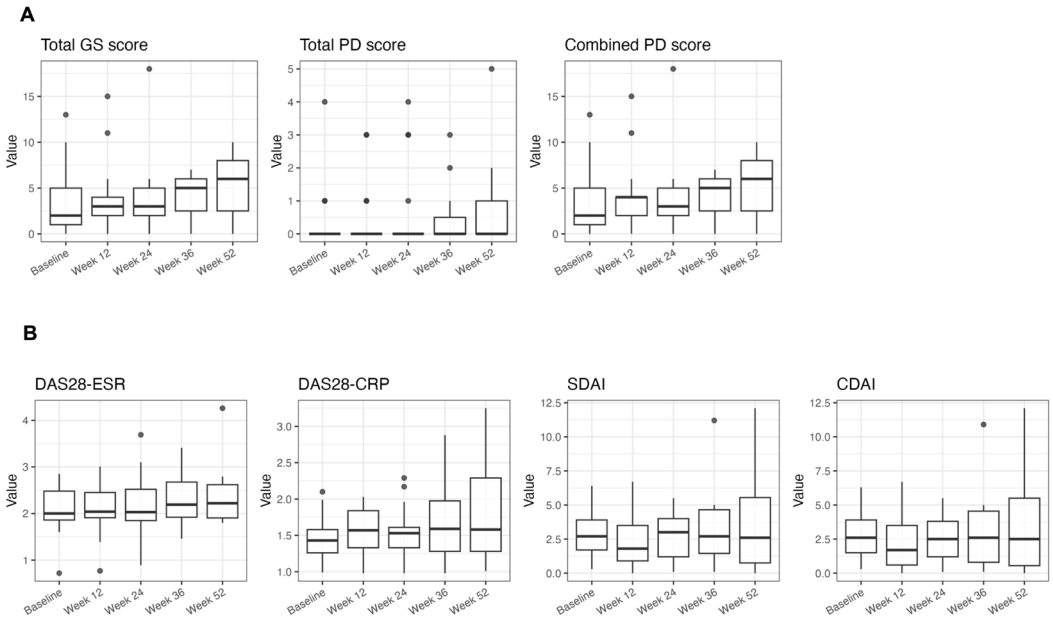

Figure 1. Changes in MSUS scores and clinical disease activity during the study period. (A) MSUS scores and **(B)** clinical disease indicies. Horizontal bar: median, boxes: 25th and 75th percentiles, bars: 5th and 95th percentiles. CDAI: clinical disease activity index, CRP: C-reactive protein, DAS28: Disease Activity Score-28, ESR: erythrocyte sedimentation rate, GS: gray scale, HAQ-DI: Health Assessment Questionnaire-Disability Index, PD: power Doppler, SDAI: simplified disease activity index.

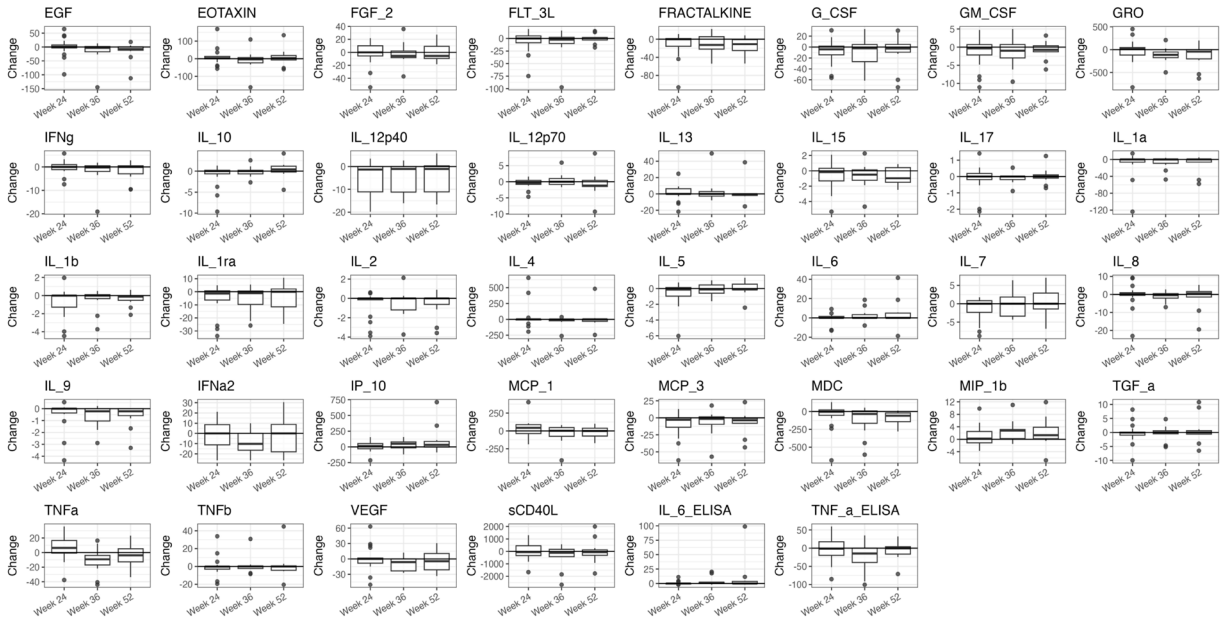

Figure 2. Multiple cytokine array results. Change in each cytokine from baseline at 24, 36, and 52 weeks. None of the changes were significant.

of bDMARD-RP is impossible because bDMARDs are polymeric compounds. Therefore, a robust pharmacovigilance database needs to be established to effectively monitor the post-marketing efficacy and safety of biosimilars. A detailed MSUS-based assessment of the efficacy of switching from etanercept-RP to etanercept biosimilars will provide valuable information, thereby helping clinicians and patients switch with confidence. Additionally, it is necessary to assess the changes in disease activity after the reduction of biosimilars. The PRESERVE study maintained low disease activity in 159 (79.1%) of 201 patients 52 weeks after etanercept was reduced to 25 mg. This study included a 28-week observation period after dose reduction, which was shorter than that of the PRESERVE study, and the results were similar. Additionally, the PRESERVE study (*9*) revealed that the proportion of patients who maintained remission after etanercept dose reduction was higher among those with deep or sustained remission. Tanaka *et al.* (*28*) demonstrated that patients

who achieved disease control following the definitions of sustained ACR/EULAR Boolean remission, CDAI remission, and sustained deep remission by DAS28 were more likely to maintain remission after dose reduction or discontinuation, as evidenced by randomized controlled trial results from studies including PRESERVE and PRIZE (*29*).

Overall, the present study revealed that most patients achieved remission levels in DAS28-ESR, DAS28-CRP, SDAI, and CDAI at baseline that were maintained, and PD remission was sustained, as assessed with MSUS. One patient who did not achieve the primary endpoint had LDA with a baseline DAS28-ESR of 2.66 and did not meet the remission criteria, although both the total GS score and total PD score at baseline were 0 on MSUS. DAS28-ESR exhibited a gradual upward trend and no longer met the LDA criteria, and both total GS and total PD scores on MSUS demonstrated a gradual upward trend after week 24 in this patient. Additionally, the serum levels of IL-6 and CXCL-10 (IP-10) were persistently elevated throughout the course (data not shown).

In this study, clinical assessments such as DAS28-ESR, DAS28-CRP, SADI, and CDAI showed little change after 24 weeks of treatment with etanercept biosimilar1 until week 52, whereas the total GS score and combined PD score of MSUS exhibited an increasing trend. This indicates that MSUS scores may reflect disease activity more accurately than clinical assessment. However, this change was not so bothersome in certain cases. Patients who achieved clinical and PD remission at baseline maintained this status, even after dose reduction of the etanercept biosimilar 1, except for one patient (data not shown). In general, patients who have not achieved clinical and/or PD remission at baseline are more likely to relapse (*30*). The present study yielded similar results.

These results indicate that patients who achieved both clinical and PD remission using etanercept-RP were more likely to remain in remission after switching to the etanercept biosimilar 1 and demonstrated a lower likelihood of relapse after dose reduction.

This study had several limitations. First, the sample size is small. Only 20 patients were registered although 62 cases were expected to be enrolled. This may be because of the absence of an inconsiderable part to the resistance of patients who were stable on etanercept-RP to switching to etanercept biosimilar 1. Concerns about the nocebo effect of switching to etanercept biosimilar 1 existed before the study; however, in the end, no particular problems were observed, as the patients were enrolled after being fully informed. Second, the present study only assessed up to 24 or 52 weeks, and further studies are warranted to enable a long-term evaluation. Third, another aim of this study was to investigate baseline assessment as a predictor of LDA/remission after switching to etanercept biosimilar 1. Owing to the limited number of relapse cases (n = 1), it was challenging to identify clear differences in baseline characteristics, clinical assessments, MSUS findings, and serum biomarkers between LDA/remission and relapse cases. However, the relapse case demonstrated persistently elevated levels of IL-6 and IP-10 throughout the course, which may have been associated with the deterioration of the MSUS scores.

This is the first report to thoroughly evaluate the efficacy of switching from etanercept-RP to etanercept biosimilar 1 with MSUS as well as the efficacy of reducing the dose of etanercept biosimilar 1 with MSUS. Switching from etanercept-RP to etanercept biosimilar 1 is feasible in patients with stable disease activity, and subsequent dose reduction. These results have considerable clinical value.

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