Modern Rheumatology, **34**, 2024, 1135–1141
DOI: https://doi.org/10.1093/mr/roae018
Advance Access Publication Date: 5 March 2024
Original Article

Comparison of safety and effectiveness between etanercept biosimilar LBEC0101 and reference in patients with rheumatoid arthritis in real-world data using the KURAMA cohort

Tomoya Kawakami[a], Sho Masui[a,b], Akira Onishi[c], Hideo Onizawa[c], Takayuki Fujii[c,d], Kosaku Murakami[e], Koichi Murata[c,d], Masao Tanaka[c], Takashi Shimada[f], Shunsaku Nakagawa[a], Shuichi Matsuda[d], Akio Morinobu[c,g], Tomohiro Terada[a] and Atsushi Yonezawa[a,b,*]

[a]Department of Clinical Pharmacology and Therapeutics, Kyoto University Hospital, Kyoto, Japan
[b]Division of Integrative Clinical Pharmacology, Faculty of Pharmacy, Keio University, Tokyo, Japan
[c]Department of Advanced Medicine for Rheumatic Diseases, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[d]Department of Orthopaedic Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[e]Center for Cancer Immunotherapy and Immunobiology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[f]SHIMADZU Corporation, Kyoto, Japan
[g]Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

*Correspondence: Atsushi Yonezawa; ayone@keio.jp; Division of Integrative Clinical Pharmacology, Faculty of Pharmacy, Keio University, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan.

ABSTRACT

Objectives: Biosimilars are anticipated to be widely used in the treatment of rheumatoid arthritis (RA), owing to their cost efficiency; LBEC0101 was the first etanercept (ETN) biosimilar approved in Japan. However, there are limited real-world data comparing its safety and effectiveness with those of a reference product.

Methods: This study used data from the Kyoto University Rheumatoid Arthritis Management Alliance cohort, including patients with RA who received ETN therapy—ETN reference product (ETN-RP) or LBEC0101—between 2015 and 2021. Serum ETN levels were measured using liquid chromatography–tandem mass spectrometry.

Results: The 1-year continuation rates of ETN-RP and LBEC0101 were 58.7% and 74.4%, respectively. Effectiveness of treatment was evaluated in 18 patients; both products significantly reduced the 28-joint RA disease activity score and erythrocyte sedimentation rate (DAS28-ESR). Moreover, to determine equivalence, we analysed 11 patients who switched from ETN-RP to LBEC0101; the DAS28-ESR and serum ETN levels before and after switching were not significantly different.

Conclusions: This real-world cohort study confirmed that the biosimilar of ETN, LBEC0101, was comparable to the reference product in terms of continuation rate, effectiveness at initiation of introduction, and effect persistence before and after switching in clinical practice.

KEYWORDS: Biosimilar; etanercept; LBEC0101; real-world data; rheumatoid arthritis

Introduction

In clinical trials, biosimilars have been demonstrated to exhibit quality, safety, and efficacy equivalent to previously approved biopharmaceutical products, also referred to as reference products [1]. Biosimilars cost less compared with reference products because fewer resources are used in development and are therefore expected to reduce treatment costs and improve patient health, particularly in the field of rheumatoid arthritis (RA) [2]. However, data related to the scope and concurrent medication use with biosimilars are limited, which concerns physicians about their use in clinical practice.

Somatropin BS, a human growth hormone biosimilar, was the first biosimilar to be approved in Japan in 2009 [3]. In 2014, an infliximab (IFX) biosimilar was approved for the treatment of RA [4]. However, the penetration rate of biosimilars in Japan is very low compared to other countries such as the UK and France—where the acceptance rate of IFX biosimilars is much higher; as of 2018, IFX biosimilars had accounted for only about 6% of the total IFX sales in Japan [5]. To accelerate the use of biosimilars, it is necessary to acquire and analyse data on their safety and effectiveness in real-world settings.

Received 5 December 2023; Accepted 23 February 2024

Etanercept (ETN) is a soluble formulation of tumour necrosis factor-α/lymphotoxin-α receptor that inhibits the action of cytokines involved in inflammation and immune response. ETN is more effective compared to methotrexate (MTX) monotherapy for RA treatment [6]. Since its approval in 2005, ETN has been used for patients with RA who have shown inadequate responses to existing treatments and its use is still continued in many patients [7]. LBEC0101, the first biosimilar to ETN, was approved in Japan in 2018. The equivalence of LBEC0101 to an ETN reference product (ETN-RP) was evaluated in a phase III study in patients with active RA despite treatment with MTX [8]. Another study analysed the sustained efficacy only in Korean patients with RA who switched from ETN-RP to LBEC0101 [9]. The results of these clinical trials demonstrated the therapeutic equivalence and safety of LBEC0101 compared to those of ETN-RP. However, these studies had some limitations: concomitant use of MTX without dose modification was required during the study period, and patients taking rheumatoid agents other than MTX were excluded from the study. In real-world clinical practice, all patients do not receive MTX or take multiple rheumatoid agents. Therefore, evaluation of the safety and effectiveness of LBEC0101 using real-word data is essential.

Therefore, this study aimed to compare the treatment persistence rates, safety, and effectiveness of ETN-RP and its biosimilar, LBEC0101, in patients with RA, using real-world data from the Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) cohort.

Materials and methods

Study design and patient selection

This was a single-centre retrospective study conducted using the KURAMA cohort database. The KURAMA cohort was established in 2011 by the Center for Rheumatic Diseases at Kyoto University Hospital to ensure strict RA control and facilitate the use of clinical and laboratory data obtained from patients during clinical investigations [10]. All patients met the classification criteria for RA established in the revised 1987 American College of Rheumatology (ACR) or the 2010 ACR/European League Against Rheumatism (EULAR) guidelines. The study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval no. R0357), and written informed consent was obtained from all participating patients.

The present study included data from the KURAMA cohort, dated between 1 January 2015 and 31 December 2021. Of the 192 patients who received ETN therapy in the cohort, 130 were excluded as they were treated prior to the study period.

Initially, 62 patients (ETN-RP, 39 patients; LBEC0101, 23 patients) were analysed for treatment persistence with ETN-RP and LBEC0101. Subsequently, 44 patients were excluded; exclusion criteria are as follows: lack of 28-joint RA disease activity score and erythrocyte sedimentation rate (DAS28-ESR) data within 12 weeks before or 24 weeks after ETN initiation or achieving clinical remission or low disease activity (DAS28-ESR ≤ 3.2) before starting ETN treatment. We further evaluated the effectiveness of ETN-RP and LBEC0101 in 18 patients (ETN-RP, 10 patients; LBEC0101, 8 patients) (Figure 1). Additionally, treatments were switched from ETN-RP to LBEC0101 in 11 patients who were then analysed for treatment equivalence. Serum ETN levels were measured in five patients.

Data collection and evaluation of disease activity

The following clinical characteristics were included for each patient: age, body weight, sex, RA disease duration, ETN treatment duration, MTX use, oral glucocorticoid use, conventional synthetic disease-modifying antirheumatic drug (csDMARD) use, tender joint count, swollen joint count, C-reactive protein (CRP) level, rheumatoid factor (RF), and anti-citrullinated protein antibody (ACPA). Actarit, aurothiomalate, auranofin, bucillamine, iguratimod, leflunomide, mizoribine, MTX, salazosulfapyridine, cyclosporine, and tacrolimus were considered csDMARDs. RA disease activity was evaluated using the clinical disease activity index (CDAI), simplified disease activity index (SDAI), physical disability by health assessment questionnaire-disability index (HAQ-DI), and DAS28-ESR. Baseline was defined as the last data point within 12 weeks of ETN initiation. Patients achieving good responses to ETN therapy were assessed according to the EULAR response criteria.

Measurement of serum ETN levels

Blood samples were collected to measure the serum levels of ETN. Serum ETN levels were measured using an LCMS-8060 quadrupole mass spectrometer (SHIMADZU, Kyoto, Japan) as previously reported, with some modifications [11–13]. Briefly, to obtain peptides from the fragment antigen-binding region of immunoglobulin G, serum samples were pretreated with the nSMOL™ Antibody BA Kit (SHIMADZU, Kyoto, Japan) according to the manufacturer's protocol.

Statistical analysis

Results are expressed as mean plus standard deviation (SD). All statistical analyses were performed using EZR statistical software, version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [14]. Persistence was compared using Kaplan–Meier survival curves and the log-rank test. The significance of the differences was tested using the Wilcoxon signed-rank test or the Mann–Whitney U test. *P*-values of $<.05$ were considered statistically significant.

Results

Comparison of persistence of ETN-RP and LBEC0101 in RA patients

We evaluated the persistence of ETN in 62 newly treated patients (ETN-RP, 39 patients; LBEC0101, 23 patients). The demographic and clinical characteristics of the patients are shown in Table 1. The proportion of female patients in both groups was ∼90%. The rates of oral glucocorticoid and csDMARDs, including MTX, showed similarity between the respective groups. Considering the censoring,

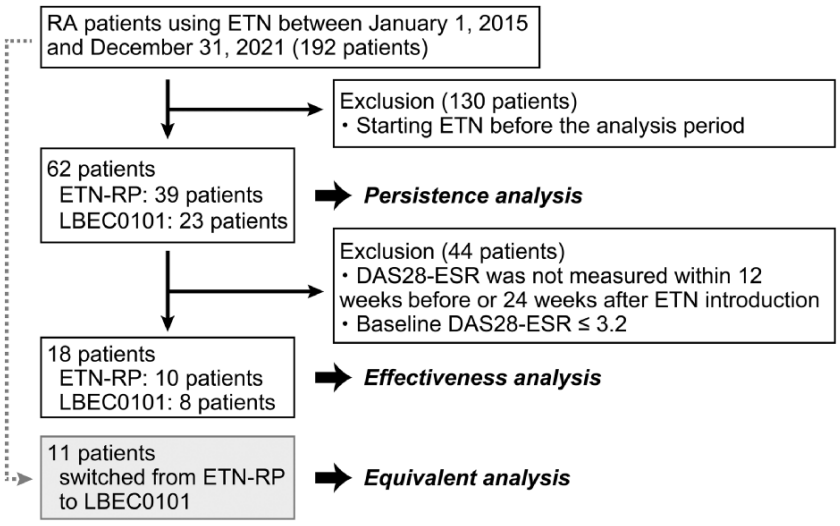

Figure 1. Study design. Flowchart depiction of patients analysed in the present study. Of the 192 patients who received ETN therapy in the KURAMA cohort between 1 January 2015 and 31 December 2021, 130 were excluded as they were treated with ETN prior to the study period. Initially, 62 patients (ETN-RP, 39 patients; LBEC0101, 23 patients) were analysed for treatment persistence. Subsequently, 44 patients were excluded; exclusion criteria are as follows: lack of DAS28-ESR data within 12 weeks before or 24 weeks after ETN initiation or achieving clinical remission or low disease activity (DAS28-ESR $\leq$ 3.2) before starting ETN treatment. We further evaluated the effectiveness of ETN-RP and LBEC0101 in 18 patients (ETN-RP, 10 patients; LBEC0101, 8 patients). Additionally, during the analysis period, 11 patients whose treatments were switched from ETN-RP to LBEC0101 were then analysed for treatment equivalence.

Table 1. Baseline characteristics of patients with RA treated with ETN-RP and LBEC0101 for treatment effect persistence analysis.

	ETN-RP (n = 39)	LBEC0101 (n = 23)
Age (years), mean (SD)	60.1 (16.5)	54.3 (18.8)
Body weight (kg), mean (SD)	56.3 (10.9)	54.2 (11.1)
Number of females, n (%)	34 (87.2)	21 (91.3)
Disease duration (years), mean (SD)	8.7 (8.5)	10.7 (7.5)
Previous use of biologics, n (%)	11 (28.2)	9 (39.1)
Abatacept, n	3	1
Adalimumab, n	3	2
ETN, n	1	0
Golimumab, n	1	2
IFX, n	1	0
Tocilizumab, n	2	4
Oral glucocorticoid use, n (%)	13 (33.3)	6 (26.1)
csDMARD use, n (%)	32 (82.1)	21 (91.3)
MTX use, n (%)	21 (53.8)	12 (52.2)
RF positive, n (%)	27 (69.2)	18 (78.3)
ACPA positive, n (%)	29 (74.4)	19 (82.6)

the 1-year continuation rate of ETN-RP was 58.7%, and for LBEC0101, it was 74.4%. No statistically significant difference was observed between the two groups (Figure 2, P = .061). However, LBEC0101 tended to have a higher persistence rate. The reasons for treatment discontinuation in RA patients treated with ETN-RP or LBEC0101 for 1 year were examined. Adverse effects leading to discontinuation were observed in seven patients (17.9%) treated with ETN-RP and one patient (4.3%) treated with LBEC0101 (Table 2).

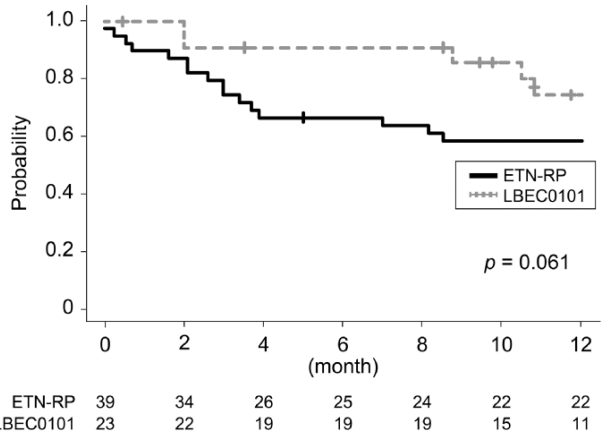

Figure 2. Persistence rate of treatment in patients with RA. Kaplan–Meier curve showing treatment persistence for ETN-RP (solid line) and LBEC0101 (dashed line). Marked points indicate censored data points; P-values were calculated using log-rank tests.

The observed adverse effects are as follows: for ETN-RP, there were two patients with infection (5.1%), four patients with injection site reactions (10.3%), and one patient with suspected heart failure (2.6%). For LBEC0101, one patient had general eczema and dryness (4.3%). The non-remission rates were similar for both products.

Comparison of the effect of ETN-RP and LBEC0101 on DAS28-ESR score in RA patients

We assessed the effectiveness of ETN in patients who received the newly initiated treatment (ETN-RP, 10 patients; LBEC0101, 8 patients). The demographic and clinical characteristics of the patients are presented in Table 3.

Table 2. Proportion of patients who discontinued treatment with ETN-RP and LBEC0101 >1 year.

	ETN-RP ($n = 39$)	LBEC0101 ($n = 23$)
Non-remission, *n* (%)	6 (15.4)	3 (13.0)
Adverse effects leading to discontinuation, *n* (%)	7 (17.9)	1 (4.3)
Infection, *n* (%)	2 (5.1)	0 (0)
Injection site reactions, *n* (%)	4 (10.3)	0 (0)
Skin disorders, *n* (%)	0 (0)	1 (4.3)
Suspected heart failure, *n* (%)	1 (2.6)	0 (0)
Others, *n* (%)	4 (10.3)	2 (8.7)

Table 3. Baseline characteristics of patients with RA newly initiated on ETN-RP and LBEC0101 treatments for effectiveness analysis.

	ETN-RP ($n = 10$)	LBEC0101 ($n = 8$)
Age (years), mean (SD)	56.0 (16.2)	47.7 (14.1)
Body weight (kg), mean (SD)	53.1 (6.8)	56.2 (10.9)
Number of females, *n* (%)	10 (100.0)	8 (100.0)
Disease duration (years), mean (SD)	9.8 (11.5)	11.0 (5.4)
Oral glucocorticoid use, *n* (%)	3 (30.0)	1 (12.5)
csDMARD use, *n* (%)	9 (90.0)	7 (87.5)
MTX use, *n* (%)	7 (70.0)	4 (50.0)
RF positive, *n* (%)	7 (70.0)	6 (75.0)
ACPA positive, *n* (%)	8 (80.0)	6 (75.0)
DAS28-ESR, mean (SD)	4.7 (0.9)	5.2 (1.0)
CRP level (mg/dl), mean (SD)	0.8 (0.8)	1.5 (1.8)
CDAI, mean (SD)	19.6 (9.2)	19.5 (10.2)
SDAI, mean (SD)	20.4 (9.3)	20.9 (10.2)
HAQ-DI, mean (SD)	0.9 (0.4)	1.1 (0.6)

Figure 3 shows the change in the DAS28-ESR score for patients who started ETN-RP and LBEC0101. Both products significantly reduced DAS28-ESR scores (ETN-RP: −2.35, LBEC0101: −2.75), and all patients achieved a good or moderate response according to the EULAR improvement criteria. No significant difference in effectiveness was found between ETN-RP and LBEC0101 using the Mann–Whitney U test ($P = .33$; Figure 3).

Changes in DAS28-ESR score and ETN concentration in RA patients who were switched from ETN-RP to LBEC0101

We assessed the DAS28-ESR scores in 11 patients who switched from ETN-RP to LBEC0101, and serum ETN levels were measured in five of these patients. The demographic and clinical characteristics of the patients are shown in Table 4. The DAS28-ESR scores before and after switching from ETN-RP to LBEC0101 were not significantly different, and the overall mean values were also not significantly different [Figure 4(a), $P = .58$]. Furthermore, there was no significant difference in serum ETN levels before and after switching in any of the five patients [Figure 4(b), $P = .13$].

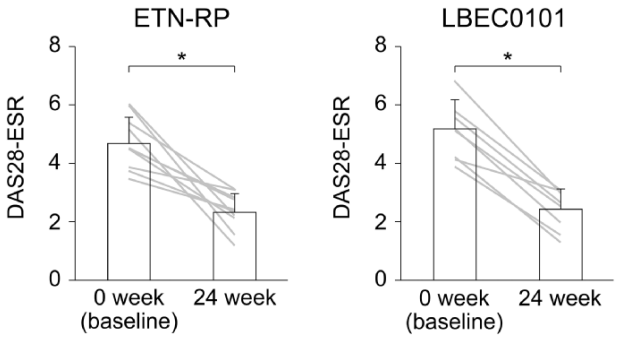

Figure 3. Effect of ETN-RP and LBEC0101 treatments on DAS28-ESR score in patients with RA. Graph shows the mean change in DAS28-ESR score from baseline to 24 weeks after initiation of treatment: ETN-RP, 10 patients; LBEC0101, 8 patients. Grey lines represent individual patient data. Data were analysed using the Wilcoxon signed-rank test; * $P < .01$.

Table 4. Baseline characteristics of patients with RA who switched from ETN-RP to LBEC0101, studied for treatment equivalence.

	$n = 11$
Age (years), mean (SD)	52.6 (14.5)
Body weight (kg), mean (SD)	56.8 (10.2)
Number of females, *n* (%)	10 (90.9)
Disease duration (years), mean (SD)	20.4 (19.2)
Duration of ETN-RP treatment (years), mean (SD)	7.1 (3.7)
Dose of ETN (25 mg/50 mg), *n* (%)	5 (45.5)/6 (54.5)
Oral glucocorticoid use, *n* (%)	2 (18.2)
csDMARD use, *n* (%)	9 (81.8)
MTX use, *n* (%)	8 (72.7)
RF positive, *n* (%)	10 (90.9)
ACPA positive, *n* (%)	10 (90.9)
DAS28-ESR, mean (SD)	3.2 (0.7)
CRP level (mg/dl), mean (SD)	0.3 (0.2)
CDAI, mean (SD)	4.3 (1.9)
SDAI, mean (SD)	4.7 (2.2)
HAQ-DI, mean (SD)	0.7 (0.8)

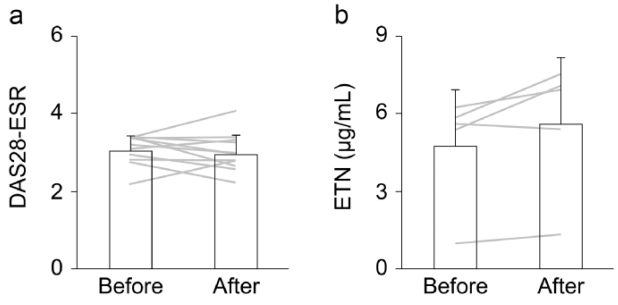

Figure 4. Changes in (a) DAS28-ESR score and (b) ETN level in patients with RA who switched from ETN-RP to LBEC0101. Graphs show mean + SD change in DAS28-ESR score ($n = 11$ patients) and serum ETN levels ($n = 5$ patients) >24 weeks, before and after switching from ETN-RP to LBEC0101. Grey lines represent individual patient data. Data were analysed using the Wilcoxon signed-rank test.

Discussion

Biosimilars have been demonstrated to have quality, safety, and efficacy equivalent to reference products in clinical trials. However, owing to the limitations of clinical trials, it is imperative to assess the safety and effectiveness of biosimilars in real-world clinical practice. There are some post-marketing

reports on the equivalence at introduction and the persistence of effectiveness after switching to ETN biosimilars, such as SB4 and gp2015 marketed in other countries [15–17]. ETN biosimilars have shown similar efficacy and treatment persistence in patients with RA in a real-life setting. Notably, there are limited data available on LBEC0101 beyond clinical reports, as it is currently marketed exclusively in Japan and South Korea. In this study, we compared the effectiveness and persistence rates of ETN-RP and LBEC0101 in patients with RA using real-world data from the KURAMA cohort. No significant difference was observed in the DAS28-ESR scores between ETN-RP and LBEC0101 patients who started treatment and switched from ETN-RP to LBEC0101. Similar data regarding the effectiveness of previous clinical trials have been obtained. In addition, switching from ETN-RP to LBEC0101 did not affect the serum drug concentration. A previous report suggested a correlation between serum ETN concentration 3 months after starting treatment and the disease activity of RA at 6 months [18]. The nocebo effect has recently attracted considerable attention in the field of biosimilars. A lack of acceptance and negative perceptions of biosimilars may enhance the nocebo effect following a switch and increase non-adherence [19, 20]. The present results on the effectiveness and serum drug concentrations can ensure the reliability of LBEC0101 in clinical practice.

Clinical trials of LBEC0101 at the developmental stage have been conducted in patients with active RA despite receiving MTX at 48 centres in Japan and 30 centres in South Korea [8]. The change in DAS28-ESR score at 24 weeks, as reported in the clinical trial, was found to be comparable with ETN-RP (−2.86) and LBEC0101 (−3.01). Moreover, an extension study of the Phase III trial, conducted solely in South Korean facilities, showed that the efficacy was sustained even after switching from ETN-RP to LBEC0101 [9]. These results were confirmed in clinical practice. In a Phase III trial [8], the inclusion criteria restricted the concomitant use of MTX without dose modification during the study period. However, our data showed that LBEC0101 was equivalent to ETN-RP in clinical practice, without the need for concomitant medications. Additionally, the equivalent effectiveness of ETN-RP and LBEC0101 was confirmed in Japanese patients. These data could contribute to the promotion of biosimilar use.

In the present analysis, we compared the continuation rates of patients with RA who were newly started on either ETN-RP or LBEC0101 and no significant differences were observed (Figure 2). However, the 1-year continuation rate was ∼16% higher with LBEC0101, which was attributed to a lower discontinuation rate owing to side effects. Notably, there was a difference in the number of patients who discontinued treatment owing to injection site reactions (ETN-RP, 10.3%; LBEC0101, 0%), which we consider to have contributed to the difference in continuation rates observed in this study. In a Phase III trial, the overall proportion of patients experiencing side effects did not significantly differ between ETN-RP and LBEC0101, although the incidence of injection site reactions was higher in ETN-RP than in LBEC0101 (erythema: 25.1% and 5.3%, pruritus: 20.3% and 3.7%, and swelling: 7.0% and 2.1% for ETN-RP and LBEC0101) [8]. Clinical trials have implied that LBEC0101 may have a lower incidence of injection site reactions than ETN-RP. Other biosimilars of ETN (SB4, GP2015, and YLB113) have also been reported to show ∼50–75% lower incidence of injection site reactions than the reference product based on the results of their clinical trials [21–23]. LBEC0101 uses a device with a thin needle, which may reduce the likelihood of injection site reactions [24]. The development of biosimilars can ensure their safety based on the latest knowledge, while ensuring equivalent efficacy. Further real-world studies are required to validate the safety of LBEC0101.

This study had some limitations. First, this was a single-centre, retrospective, observational study, and the number of cases analysed was limited. To reduce accident errors, we analysed the data from three perspectives and obtained similar data. Second, the time from the initiation of ETN products to evaluation varied among patients, owing to the retrospective cohort study. The time was limited to 24 weeks after introduction or switching to minimize the influence of other factors. Third, the analysis of the effectiveness of ETN treatment initiation was based solely on female patients for both products. In Japan, RA is more common in women, with a male-to-female ratio of ∼1:3 [25]. The high proportion of females in this analysis was not considered a major issue. Fourth, LBEC0101 tended to have a higher proportion of recent patient data than ETN-RP. It is important to acknowledge that discontinuation criteria and treatment options vary over time. Although we aimed to use relatively recent data from 2015 for this analysis, it is important to acknowledge that this time frame may not completely capture the evolving landscape of clinical practice.

In conclusion, this real-world cohort study confirmed that the biosimilar of ETN, LBEC0101, was comparable to the reference product in terms of continuation rate, effectiveness at initiation of introduction, and effect persistence before and after switching in clinical practice. Although higher safety of biosimilars can also be speculated, further examination in the future is necessary.

Acknowledgements

The authors are grateful to Dr Akiko Ishii-Watabe (National Institute of Health Sciences, Kawasaki, Japan) for advice on this study and Ms Kotoko Yokoyama (Shimadzu, Kyoto, Japan) for support in measuring ETN concentrations, and thank all the medical staff of the Rheumatic Disease Center, Kyoto University Hospital.

Conflict of interest

The Department of Advanced Medicine for Rheumatic Diseases was supported by two local governments (Nagahama City, Shiga, and Toyooka City, Hyogo, Japan) and two pharmaceutical companies (Asahi Kasei Pharma Corp. and AYUMI Pharmaceutical Co.). The KURAMA cohort study was supported by a grant from Daiichi Sankyo Co., Ltd. A.O. received grants from Pfizer Inc., Bristol Myers Squibb, and Advantest, as well as personal fees from Asahi Kasei Pharma Corp., Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan K.K, Ono Pharmaceutical Co., Mitsubishi Tanabe Pharma Co., Eisai Co. Ltd, AbbVie Inc., and Daiichi Sankyo Co. Ltd; T.F. received speaking fees from Eisai Co. Ltd, Asahi Kasei Pharma Corp., AbbVie Inc., and Janssen Pharmaceutical

K.K.; K. Murak. received speaker's fees and/or consulting fees from Eisai Co. Ltd, Chugai Pharmaceutical Co. Ltd., Pfizer Inc., Bristol-Myers Squibb, Mitsubishi Tanabe Pharma Corporation, UCB Japan Co. Ltd, Daiichi Sankyo Co. Ltd, and Astellas Pharma Inc.; K.Murat. received speaking fees and/or consulting fees from Eisai Co. Ltd, Chugai Pharmaceutical Co. Ltd., Asahi Kasei Pharma Corp., Bristol Myers Squibb, Mitsubishi Tanabe Pharma Co., Janssen Pharmaceutical K.K., and Daiichi Sankyo Co. Ltd; M.T. received research grants and speaking fees from AbbVie Inc., Asahi Kasei Pharma Corp., Astellas Pharma Inc., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd, Eisai Co. Ltd, Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., Kyowa Kirin Co. Ltd, Pfizer Inc., Taisho Pharmaceutical Co. Ltd, Mitsubishi Tanabe Pharma Co., Teijin Pharma Ltd, and UCB Japan Co. Ltd; S.Mat. received speaking fees from Pfizer Inc., Chugai Pharmaceutical Co. Ltd., Asahi Kasei Pharma Corp., Eisai Co. Ltd, Mitsubishi Tanabe Pharma Corp., and Teijin Pharma Ltd; A.M. received honoraria from AbbVie G.K., Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., Eisai Co. Ltd, Pfizer Inc., Bristol Myers Squibb, Mitsubishi Tanabe Pharma Co., Astellas Pharma Inc., and Gilead Sciences, Japan, and received research grants from AbbVie G.K., Asahi Kasei Pharma Corp., Chugai Pharmaceutical Co. Ltd., and Mitsubishi Tanabe Pharma Co.; T.T. received speaking fees from Daiichi Sankyo Co. Ltd and Chugai Pharmaceutical Co. Ltd.; A.Y. received research grants from Shimadzu Corporation and AYUMI Pharmaceutical Co. The remaining authors report that there are no competing interests to declare.

Funding

This work was supported in part by a Grant-in-Aid for Scientific Research (B) (KAKENHI) from the Japan Society for the Promotion of Science under grant numbers 19H03389 and 23H02649, the Japan Agency for Medical Research and Development (AMED) under grant number 21mk0101152h0503, and the Nakatomi Foundation, to A.Y.

References

[1] Zuñiga L, Calvo B. Biosimilars: pharmacovigilance and risk management. *Pharmacoepidemiol Drug Saf* 2010;**19**:661–9.
[2] Dörner T, Strand V, Cornes P *et al*. The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016;**75**:974–82.
[3] Farhat F, Torres A, Park W *et al*. The concept of biosimilars: from characterization to evolution—a narrative review. *Oncologist* 2018;**23**:346–52.
[4] Tanaka Y, Yamanaka H, Takeuchi T *et al*. Safety and efficacy of CT-P13 in Japanese patients with rheumatoid arthritis in an extension phase or after switching from infliximab. *Mod Rheumatol* 2017;**27**:237–45.
[5] Kim Y, Kwon HY, Godman B *et al*. Uptake of biosimilar infliximab in the UK, France, Japan, and Korea: budget savings or market expansion across countries? *Front Pharmacol* 2020;**11**:970.
[6] Bathon JM, Martin RW, Fleischmann RM *et al*. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;**343**:1586–93.
[7] Koike T, Harigai M, Inokuma S *et al*. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. *J Rheumatol* 2009;**36**:898–906.
[8] Matsuno H, Tomomitsu M, Hagino A *et al*. Phase III, multicentre, double-blind, randomised, parallel-group study to evaluate the similarities between LBEC0101 and etanercept reference product in terms of efficacy and safety in patients with active rheumatoid arthritis inadequately responding to methotrexate. *Ann Rheum Dis* 2018;**77**:488–94.
[9] Park MC, Matsuno H, Kim J *et al*. Long-term efficacy, safety and immunogenicity in patients with rheumatoid arthritis continuing on an etanercept biosimilar (LBEC0101) or switching from reference etanercept to LBEC0101: an open-label extension of a phase III multicentre, randomised, double-blind, parallel-group study. *Arthritis Res Ther* 2019;**21**:122.
[10] Terao C, Hashimoto M, Yamamoto K *et al*. Three groups in the 28 joints for rheumatoid arthritis synovitis—analysis using more than 17,000 assessments in the KURAMA database. *PLoS One* 2013;**8**:e59341.
[11] Iwamoto N, Shimada T, Umino Y *et al*. Selective detection of complementarity-determining regions of monoclonal antibody by limiting protease access to the substrate: nanosurface and molecular-orientation limited proteolysis. *Analyst* 2014;**139**:576–80.
[12] Iwamoto N, Takanashi M, Yokoyama K *et al*. Multiplexed monitoring of therapeutic antibodies for inflammatory diseases using Fab-selective proteolysis nSMOL coupled with LC-MS. *J Immunol Methods* 2019;**472**:44–54.
[13] Iwamoto N, Yokoyama K, Takanashi M *et al*. Application of nSMOL coupled with LC-MS bioanalysis for monitoring the Fc-fusion biopharmaceuticals etanercept and abatacept in human serum. *Pharmacol Res Perspect* 2018;**6**:e00422.
[14] Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013;**48**:452–8.
[15] Cantini F, Benucci M. Focus on biosimilar etanercept – bioequivalence and interchangeability. *Biologics* 2018;**12**:87–95.
[16] Codreanu C, Popescu CC, Mogosan C *et al*. Efficacy and safety of original and biosimilar etanercept (SB4) in active rheumatoid arthritis – a comparison in a real-world national cohort. *Biologicals* 2019;**62**:27–32.
[17] Carballo N, Pérez García C, Grau S *et al*. Real-world effectiveness and persistence of reference etanercept versus biosimilar etanercept GP2015 among rheumatoid arthritis patients: a cohort study. *Front Pharmacol* 2022;**13**:980832.
[18] Daïen CI, Daïen V, Parussini E *et al*. Etanercept concentration in patients with rheumatoid arthritis and its potential influence on treatment decisions: a pilot study. *J Rheumatol* 2012;**39**:1533–8.
[19] Petit J, Antignac M, Poilverd RM *et al*. Multidisciplinary team intervention to reduce the nocebo effect when switching from the originator infliximab to a biosimilar. *RMD Open* 2021;**7**:e001396.
[20] Odinet JS, Day CE, Cruz JL *et al*. The biosimilar nocebo effect? A systematic review of double-blinded versus open-label studies. *J Manag Care Spec Pharm* 2018;**24**:952–9.
[21] Emery P, Vencovský J, Sylwestrzak A *et al*. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;**76**:51–7.

[22] Matucci-Cerinic M, Allanore Y, Kavanaugh A *et al*. Efficacy, safety and immunogenicity of GP2015, an etanercept biosimilar, compared with the reference etanercept in patients with moderate-to-severe rheumatoid arthritis: 24-week results from the comparative phase III, randomised, double-blind EQUIRA study. *RMD Open* 2018;**4**:e000757.

[23] Yamanaka H, Kamatani N, Tanaka Y *et al*. A comparative study to assess the efficacy, safety, and immunogenicity of YLB113 and the etanercept reference product for the treatment of patients with rheumatoid arthritis. *Rheumatol Ther* 2020;**7**: 149–63.

[24] Song YW, Park YB, Kim J. LBEC0101, an etanercept biosimilar for the treatment of rheumatoid arthritis. *Expert Opin Biol Ther* 2021;**21**:1–8.

[25] Kojima M, Nakayama T, Tsutani K *et al*. Epidemiological characteristics of rheumatoid arthritis in Japan: prevalence estimates using a nationwide population-based questionnaire survey. *Mod Rheumatol* 2020;**30**:941–7.