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The retrospective evaluation of efficacy and safety data after switching from originator rituximab to biosimilar rituximab (CT-P10) in patients diagnosed with systemic lupus erythematosus: a single-center experience

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Abstract. – OBJECTIVE: In our study, we analyzed the efficacy and safety data of patients with systemic lupus erythematosus (SLE) after switching to biosimilar rituximab (RTX).

PATIENTS AND METHODS: **Twenty-two patients who switched to RTX were included in the study. Efficacy data were analyzed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, and safety data were analyzed using the frequency of side effects.**

RESULTS: **The mean treatment duration of originator RTX was 35.6 ± 23.0 months, and the median treatment duration of biosimilar RTX was 17 months. The SLEDAI-2K score, approximately three months after the first dose of biosimilar RTX, was significantly lower (p = 0.027). A statistically significant difference was found between the SLEDAI-2K score assessed at the follow-up visit three months after the last dose of originator RTX and the SLEDAI-2K score obtained approximately three months after the first dose of biosimilar RTX (p = 0.011) and the calculated median SLEDAI-2K score was significantly lower than the SLEDAI-2K score assessed after administration of originator RTX. The side effect frequency that developed during the treatment of originator RTX was 15.3 per 100 patient-years. The most common side effect was infection, which was 15.3 per 100 patient-years. The most frequent infection was urinary tract infection. The side effect frequency during treatment of biosimilar RTX was 39 per 100 patient-years, and the most frequent infection was pneumonia.**

CONCLUSIONS: **In our study, SLEDAI-2K scores demonstrated that no efficacy loss was experienced after switching to CT-P10 molecule, which is a biosimilar RTX. It was observed that switching to biosimilar RTX did not decrease treatment efficacy in the patient group diagnosed with SLE and biosimilar RTX was found to be safe.**

Key Words:
Systemic lupus erythematosus, Rituximab, Biosimilar, Switching, SLEDAI-2K.

Introduction

Non-steroid anti-inflammatory drugs (NSAIDs), steroids, conventional disease-modifying antirheumatic drugs (c-DMARDs) (hydroxychloroquine, methotrexate, leflunomide, sulfasalazine), and immunosuppressive drugs (azathioprine, mycophenolate mofetil, cyclophosphamide, tacrolimus) can be used in the treatment of systemic lupus erythematosus (SLE). Particularly steroids and immunosuppressive drugs are associated with mortality and morbidity[1].

B cells have an important role in the pathogenesis of SLE. B cells induce T cells by acting as antigen-presenting cells and consequently induce T cells to produce cytokines. The produced cytokines of T cells stimulate B cells for the production of autoantibodies. Evidence[2] has demonstrated that a decrease in the B-cell count has a positive effect on SLE. Rituximab (RTX), which has an important place in the treatment of SLE, is a chimeric monoclonal antibody that induces apoptosis of B cells by killing B cells mediated by complement- and antibody-dependent cellular cytotoxicity by antagonizing CD20[3]. The primary endpoint could not be reached in two placebo-controlled randomized studies[4,5] related to the use of RTX in moderate and severe SLE patients. However, many studies[6-12] have reported that it can be used effectively and safely in refractory SLE patients, particularly with renal, hematological, and neurological system involvement.

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The concept of biosimilarity is considered if a molecule has a comparable quality, safety, and efficacy with the originator molecule. Biomolecules are important biotechnological products that are also available for RTX molecules, which are important members of the anti-CD20 treatment[13]. CT-P10 molecule is a biosimilar of rituximab molecule in terms of its primary structure, post-translational modifications, and biological activities. CT-P10 is the first biosimilar RTX that obtained market approval from the European Medicines Agency (EMA)[14], and its usage approval is available for all indications of originator RTX. Although there are some studies in the literature that compared originator RTX and biosimilar RTX in RA patients and presented real-life data, there was only one study[15] that was conducted in SLE patients and compared originator RTX with biosimilar RTX by presenting real-life data.

The objective of our study was to analyze the efficacy and safety data of treatments with originator RTX and CT-P10 molecules intra-comparatively and also after switching medication in the patients who mandatorily switched from originator RTX to biosimilar RTX (CT-P10) during the follow-up process under-diagnosis of SLE, and to comprehensively discuss the factors affecting the development of the side effects.

Patients and Methods

Patient Population

The study included 22 patients aged over 18 years diagnosed with SLE according to the criteria of 2012 Systemic Lupus International Collaborating Clinics (SLICC; https://sliccgroup.org/research/sle-criteria/). All of these patients mandatorily switched to biosimilar RTX after the medicine was purchased by the healthcare provider while they were under treatment with the originator RTX. They received treatments with RTX molecules for at least one course (on the 1st and 15th days). RTX protocol was adjusted to administer one course on the 1st and 15th days for every 6 months, and the RTX dose ranged between 500-1,000 mg.

Study Design

Several parameters of 22 patients who were followed-up with diagnosis of SLE between January 1995 and December 2022 in a tertiary hospital, such as age, gender, date of diagnosis, organ and system involvements, accompanying comorbidities [such as diabetes mellitus (DM), hypertension (HT), chronic kidney disease (CKD), coronary artery disease (CAD), heart failure (HF), hyperlipidemia (HL)], medication history, onset dates of the treatments with originator and biosimilar RTX, durations of treatments with originator and biosimilar RTX, antinuclear antibody (ANA), ANA profile (centromer-B, ribosomal P, dsDNA, SS-A, SS-B, Ro-52, Histon, Sm, Scl-70, Jo-1, nRNP/Sm, nucleosome, PCNA, PML- Scl), amount of steroid dose administered in switching to biosimilar molecule, side effects which developed under treatment with originator RTX, side effects which developed during treatment with biosimilar RTX, history of infections requiring hospitalization, administered immunosuppressive therapies except RTX (azathioprine, mycophenolate mofetil, tacrolimus, cyclophosphamide, cyclosporine) and administered c-DMARDs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine) were retrospectively analyzed. The findings obtained in the patient visit just prior to the last dose of originator RTX and the first visit performed on an average of three months after receiving the last dose of originator RTX, as well as the findings of the patient visits performed just prior to an average of three months after switching to biosimilar RTX were separately evaluated.

SLEDAI-2K score used for activity assessment in our study is one of the disease activity assessment tools used in patients diagnosed with SLE. A weighted scoring analysis is performed based on the presence of neurological, psychiatric, and vasculitic involvements, pleural and pericardial involvements, fever, vasculitis, cutaneous, articular and muscular involvements, urinary cast, complement levels, anti-ds-DNA positivity, presence of leukopenia and thrombocytopenia, consequently disease activity is interpreted according to the result[16,17]. Therefore, SLEDAI-2K scores assessed in the patient visit just prior to the last dose of originator RTX and the first visit performed on an average of three months after receiving the last dose of originator RTX and SLEDAI-2K scores assessed just prior to and in the first visit performed on an average of three months after switching to biosimilar RTX were evaluated for disease activity assessment and compared. The factors affecting the side effects were separately evaluated for both medicines. Ethical approval (No. 2023-5/9) was obtained on 7th March 2023 from Uludağ University Faculty of Medicine

Clinical Research Ethics Committee, Bursa, Turkey. The Uludağ University Faculty of Medicine Clinical Research Ethics Committee also approved the publication of data generated from this study. The study was conducted following the Helsinki Declaration and its latest amendments.

Statistical Analysis

After the sociodemographic, clinical, and laboratory features of the patients were determined by descriptive statistics, the distribution of the quantitative variables was identified with Shapiro-Wilk and Kolmogorov-Smirnov tests. The normally distributed data were given as mean, standard deviation, minimum, and maximum values, while non-normally distributed variables were presented as median, 25th, and 75th percentile values. Normally distributed quantitative data were analyzed using a paired-samples *t*-test, while non-normally distributed data were analyzed using the Wilcoxon test. Mc-Nemar's test was used to collect qualitative data. In addition, the factors affecting the development of side effects were analyzed using univariable and multivariable regression analysis. SPSS (IBM Corp. Released 2021. SPSS Statistics for Windows, Version 28.0.0.0; IBM Corp., Armonk, NY, USA) software was used for all statistical analyses. A $p < 0.05$ value was accepted as statistically significant.

Results

Of the patients, 86.4% were females, the mean age was 40.3 ± 10.6 years, and the mean age at diagnosis was 26.7 ± 9.4 years. The median disease duration was 11.5 years, the mean treatment duration of originator RTX was 35.6 ± 23.0 months, and the median treatment duration of biosimilar RTX was 17 months. All the patients were ANA positive. Nucleosome positivity demonstrated the highest frequency which was 50% in the analysis of the ANA profile. SS-A and ds-DNA were the second most frequently identified antibodies (31.8%). Antiphospholipid antibody syndrome (APS) was found in 18.2% of patients, while 9.1% of the patients were under follow-up with a diagnosis of idiopathic thrombocytopenic purpura (ITP) before the diagnosis of SLE. At least one comorbidity was present in 68.2% of the patients. The most frequently observed comorbidity was HT, with 63.6%. At least one system and/or organ involvement (kidney, lung, neurological, cardiac, vascular, psychiatric involvements) was present in 77.3% of the patients. The most frequently involved organ was the kidney, 63.6%. Neurological involvement was observed with a rate of 36.4%. The most common neurological involvement pattern was ischemic cerebrovascular accident (CVA) (22.7%). There were 31.8% of patients with cardiac involvement, and the most common cardiac involvement pattern was pericardial effusion with 18.2%. Thrombocytopenia (platelet < 100,000) was present in 45.5% of the patients, whereas 36.4% of the patients had serious thrombocytopenia (platelet < 50,000). The median count of the c-DMARDs used in the treatment was 2. The mean number of the administered immunosuppressive medicines except RTX was 2.4 ± 1.1. The median dose value of the steroid administered when switching to biosimilar RTX was 5 mg (Table I).

The efficacies of originator RTX and biosimilar RTX were compared by calculating SLEDAI-2K scores. Primarily, the efficacy of originator RTX was evaluated by comparing SLEDAI-2K scores obtained just before and approximately three months after administering the last dose of originator RTX. The median SLEDAI-2K score just prior to the administration of the last dose of originator RTX was 2, whereas the median SLEDAI-2K score of originator RTX assessed approximately three months after the administration of the last dose was 2.5. No statistical significance was found between the two values ($p = 0.765$). The median values of SLEDAI-2K scores assessed just prior to and approximately three months after the administration of the first dose of biosimilar RTX were 2 and 0, respectively. A statistically significant difference was found between the SLEDAI-2K scores of biosimilar RTX ($p = 0.027$). The SLEDAI-2K score calculated during the visit three months after the first dose of biosimilar RTX was significantly lower. A statistically significant difference was determined between the SLEDAI-2K score (median = 2.5) assessed in the patient visit performed three months after the last dose of originator RTX and the SLEDAI-2K score (median = 0) assessed in the patient visit performed approximately three months after the first dose of biosimilar RTX ($p = 0.011$). The median SLEDAI-2K score calculated after the administration of biosimilar RTX was significantly lower than the SLEDAI-2K score assessed after the administration of originator RTX (Table II). The side effect frequency during the administration of originator RTX was

Table I. The features of SLE patients who switched from originator rituximab to biosimilar rituximab (n = 22).

Age (years), Mean±Std. Dev. (Min, Max, Median)	40.3 ± 10.6 (23, 57, 41.5)
Gender, Female/Male	19/3 (86.4)
Age at diagnosis (years), Mean±Std. Dev. (Min, Max, Median)	26.7 ± 9.4 (13, 49, 25)
Disease duration (years), median (P_{25}, P_{75})	11.5 (8.75, 15.5)
History of APS, n (%)	4 (18.2)
Diagnosis of ITP before SLE, n (%)	2 (9.1)
IVIG treatment, n (%)	5 (22.7)
ANA positivity, n (%)	22 (100)
Ribosomal-P, n (%)	5 (22.7)
Histon, n (%)	4 (18.2)
ds-DNA, n (%)	7 (31.8)
Jo-1, n (%)	1 (4.5)
SS-A, n (%)	7 (31.8)
SS-B, n (%)	3 (13.6)
Sm, n (%)	4 (18.2)
n RNP/Sm, n (%)	5 (22.7)
PCNA, n (%)	1 (4.5)
Nucleosome, n (%)	11 (50)
PML-Scl, n (%)	1 (4.5)
Ro-52, n (%)	6 (27.3)
Presence of comorbidity, n (%)	15 (68.2)
HT, n (%)	14 (63.6)
CKD, n (%)	3 (13.6)
DM, n (%)	5 (22.7)
CAD, n (%)	1 (4.5)
HF, n (%)	1 (4.5)
Hyperlipidemia, n (%)	3 (13.6)
System and/or organ involvement, n (%)	17 (77.3)
Kidney involvement, n (%)	14 (63.6)
Lung involvement, n (%)	5 (22.7)
Pleural effusion, n (%)	5 (22.7)
Alveolar haemorrhage, n (%)	2 (9.1)
Neurological involvement, n (%)	8 (36.4)
CVA, n (%)	5 (22.7)
Transverse myelitis, n (%)	2 (9.1)
Posterior reversible encephalopathy syndrome, n (%)	1 (4.5)
Cardiac involvement, n (%)	7 (31.8)
Pericarditis, n (%)	2 (9.1)
Pericardial effusion, n (%)	4 (18.2)
Bundle branch block, n (%)	1 (4.5)
Vascular involvement, n (%)	3 (13.6)
Deep vein thrombosis, n (%)	2 (9.1)
Thrombophlebitis, n (%)	1 (4.5)
Lupus psychosis, n (%)	1 (4.5)
History of splenectomy, n (%)	1 (4.5)
Thrombocytopenia, n (%)	10 (45.5)
Serious thrombocytopenia, n (%)	8 (36.4)
Number of c-DMARDs, median (P_{25}, P_{75})	2 (1, 2)
Use of immunosuppressive treatment, N (%)	22 (100)
Azathioprine, n (%)	15 (68.2)
MMF, n (%)	15 (68.2)
Cyclosporine, n (%)	4 (18.2)
Cyclophosphamide, n (%)	13 (59.1)
Tacrolimus, n (%)	7 (31.8)
Number of used immunosuppressive medicines, Mean±Std. Dev. (Min, Max, Median)	2.4 ± 1.1 (0, 4, 2.5)
Treatment duration of originator RTX (months), Mean±Std. Dev. (Min, Max, Median)	35.6 ± 23.0 (0, 78, 34)
Treatment duration of biosimilar RTX (months), Median (P_{25}, P_{75})	17 (6.75, 20)
Steroid dose administered in switching to biosimilar RTX (mg), Median (P_{25}, P_{75})	5 (5, 5)

SLE: systemic lupus erythematosus, IVIG: intravenous immunoglobulin, ANA: antinuclear antibodies, P_{25}: 25th percentile P_{75}: 75th percentile, Std. Dev: Standard Deviation, Min: minimum, Max: maximum, ITP: idiopathic thrombocytopenic purpura, RTX: rituximab, APS: antiphospholipid syndrome, HT: hypertension, CKD: chronic kidney disease, DM: diabetes mellitus, CAD: coronary artery disease, HF: heart failure, CVA: cerebrovascular accident, c-DMARD: conventional disease modifying antirheumatic drugs, b-DMARD: biological disease modifying antirheumatic drugs, MMF: mycophenolate mofetil.

Table II. SLEDAI-2K scores of the patient groups diagnosed with SLE who switched from originator RTX to similar RTX (n = 22).

	o-RTX prior to the last dose	o-RTX after the last dose	*p*-value*	b-RTX prior to the last dose	b-RTX after the last dose	*p*-value*	o-RTX after the last dose	b-RTX after the last dose	*p*-value*
	Median; (P_{25}, P_{75})	Median; (P_{25}, P_{75})		Median; (P_{25}, P_{75})	Median; (P_{25}, P_{75})		Median; (P_{25}, P_{75})	Median; (P_{25}, P_{75})	
SLEDAI-2K	2; (0, 6)	2.5; (0, 6.5)	0.765†	2; (0, 6.5)	0; (0, 6)	**0.027**†	2.5; 0, 6.5	0; 0, 6	**0.011**†

*: $p < 0.05$ value was accepted as statistically significant. †: Wilcoxon signed ranks test. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, RTX: rituximab, o-RTX: originator RTX, b-RTX: biosimilar RTX, SLE: systemic lupus erythematosus, P_{25}: 25th percentile, P_{75}: 75th percentile.

15.3 per 100 patient-years. All the patients who developed side effects had a history of infection at least once. One patient developed urticaria as an allergic reaction. The most frequent infection was urinary tract infection (7.7 per 100 patient-years). The side effect frequency during the administration of biosimilar RTX was 39 per 100 patient-years. No allergic reaction was observed with biosimilar RTX and an infection developed due to the medicine at least once in all the patients. The most frequent infection was pneumonia, 19.5 per 100 patient-years. Since the COVID-19 pandemic was experienced at the time period of mandatory switching to biosimilar RTX, the number of patients that developed an infection due to COVID-19 was 27.3 per 100 patient-years. The most common infection type that developed secondary to COVID-19 was pneumonia (11.7 patients per 100 patient-years) and non-pneumonic lower respiratory tract infections (11.7 patients per 100 patient-years) (Table III).

No statistical significance was encountered between the frequencies of the side effects that developed during the administration of originator RTX and the side effects that developed during the administration of biosimilar RTX (p = 1.000). Additionally, no statistically significant difference was present between the development of infection (p = 1.000) and allergic reaction (p = 1.000) out of the side effects. Among the factors that influence the side effects developing during the administration of originator and biosimilar RTX age, gender, age at diagnosis, disease duration, history of APS, presence of diagnosed ITP before SLE, intravenous immunoglobulin (IVIG) treatment, ANA profile (Ribosomal P, Histon, dsDNA, SS-A, SS-B, Sm, n RNP/Sm, nucleosome, Ro-52), presence of comorbidity (HT, CKD, DM), system and/or organ involvement (lung involvement, kidney involvement, neurological involvement, cardiac involvement, vascular involvement), presence of thrombocytopenia, number of the used c-DMARDs, type of the immunosuppressive medicines (azathioprine, mycophenolate mofetil, cyclosporine, cyclophosphamide, tacrolimus), number of the immunosuppressive medicines, administration of originator RTX, administration of biosimilar RTX and dose of the steroid used in switching to biosimilar RTX were evaluated with logistic regression analysis. Univariate analysis of the factors that may influence the side effects developing during the administration of originator RTX revealed a relationship only between thrombocytopenia (platelet < 100,000/L) and the development of side effects (p = 0.041). No relationship was

Table III. The side effect frequencies that developed during the administration of originator rituximab and biosimilar rituximab (n = 22).

	Number of patients per 100 patient-years	n (%)		Number of patients per 100 patient-years	n (%)
Side effect that developed due to originator rituximab (RTX)	15.3	10 (45.5)	**Side effect that developed due to biosimilar rituximab (RTX)**	39	10 (45.5)
Allergic reaction	1.5	1 (4.5)	**Infection**	39	10 (45.5)
Urticaria	1.5	1 (4.5)	**Upper respiratory tract infection**	3.9	1 (4.5)
Infection	15.3	10 (45.5)	**Due to COVID-19**	3.9	1 (4.5)
Upper respiratory tract infection	1.5	1 (4.5)	**Lower respiratory tract infection (Non-pneumonic)**	11.7	3 (13.6)
Pneumonia	6.1	4 (18.2)	**Due to COVID-19**	11.7	3 (13.6)
Urinary tract infection	7.7	5 (22.7)	**Pneumonia**	19.5	5 (22.7)
The presence of infection history requiring hospitalization	6.1	4 (18.2)	**Due to COVID-19**	11.7	3 (13.6)
			Urinary tract infection	3.9	1 (4.5)
			The presence of infection history requiring hospitalization	15.6	4 (18.2)

encountered between the development of side effects and the analyzed factors in the univariate analysis of the factors that may influence the side effects developing during the administration of biosimilar RTX.

Discussion

In our study, which presented the retrospective real-life data of 22 patients diagnosed with SLE under single-center follow-up who switched from originator RTX to CT-P10 molecule, which is a biosimilar RTX, it was demonstrated by the calculated SLEDAI-2K scores that no efficacy loss was encountered due to switching to biosimilar RTX. It was found by comparing SLEDAI-2K scores calculated in the visits prior to and after the administration of the first dose that biosimilar RTX was effective. Although no statistically significant efficacy was monitored by the intra-comparison between the administrations of originator RTX, no efficacy loss was encountered in the evaluation of the clinical and laboratory results separately. No statistically significant difference was observed between the two drugs in terms of side effect frequencies and types regarding product safety data.

In a Phase I randomized controlled study[18] conducted in rheumatoid arthritis (RA) patients, pharmacokinetic bioequivalence between the CT-P10 molecule and originator RTX during the 24-week treatment was shown. By prolonging the patients' follow-up process until the 72nd week, it was exhibited that originator RTX and CT-P10 molecules have comparable efficacy and safety[19].

In a study[15] switching from originator RTX to biosimilar RTX that evaluated 32 patients presented with real-life data, age (mean ± std dev, 36.75 ± 15.22 years) and disease duration (median, 9.5 years) were lower, whereas the rate of the female patients (90.6%) was relatively higher compared with our study. It was observed in the same study[15] that all the patients had ANA positivity according to the analysis of laboratory features. Likewise, in the same study[15], anti-ds DNA and anti-Sm were positive with a higher rate of 56.25% and a lower rate of 9.38% compared with our study, respectively. In another double-blind, randomized study[4] that evaluated the efficacy of RTX treatment on SLE patients, the mean age was 40.2 ± 11.4 years, similar to our study in the group that received RTX treatment, whereas the disease duration of 8.5 ± 7.2 years was shorter than our study. The rate of female patients was relatively higher than in our study.

In a study[7] that involved French Autoimmunity and Rituximab (AIR) registry data and evaluated the efficacy and safety of RTX in patients diagnosed with SLE and treated with originator RTX, organ and system involvements of the patients were the following: kidney involvement 31%, central nervous system involvement (CNS) 7%, pulmonary involvement 1%, serositis 13% and hematological involvement 27%. In our study, the analysis carried out for the specific organ and system involvements requiring the administration of RTX revealed that the rates of kidney involvement and neurological involvement affecting CNS were higher. It was additionally determined that approximately 50% of the study patients were affected by both pleural and pericardial effusions in the context of serositis as well as pleuritis and pericarditis, whereas only 7% of patients were found to be affected if only pleuritis and pericarditis were evaluated.

In our study, the number of immunosuppressive drugs administered before RTX treatment was 2.4 ± 1.1, whereas that parameter was 1.72 ± 0.13 a previous study[15]. In the same study, the most frequently seen comorbidities were HT (25 %) and dyslipidemia (25%), whereas HT (63.6%) and DM (22.7%) were the most common comorbidities in our study. The rate of IVIG treatment in our study was higher compared with IVIG treatment at a rate of 12.5% in Pongtarakulpanit et al[15].

In our study, efficacy was evaluated by calculating SLEDAI-2K scores. In a study[7] that involved AIR registry data and evaluated the efficacy and safety of RTX in the patients who were diagnosed with SLE and treated with originator RTX, SELENA-SLEDAI assessment revealed a decrease in the general response of 80/113 (71%) patients (≥ 3 decrease in SELENA-SLEDAI score) and a statistically significant decrease in the mean SELENA-SLEDAI score (mean ± std. dev; 10.8 ± 8.8 to 3.4 ± 5.2) ($p < 0.0001$). In our study, although no statistically significant decrease was found between the SLEDAI-2K scores assessed prior to and three months after the last dose of originator RTX, most of the patients were found to gain treatment benefits based on clinical and laboratory outcomes. In a study[15] that evaluated the efficacy of biosimilar RTX using SLEDAI-2K score, general treatment response was assessed to be 25%, and a statistically significant decrease was monitored at the sixth month compared with the beginning ($p < 0.005$). Our study was designed with different modeling

based on SLEDAI-2K scores without discrimination between system and organ involvements. A decrease reaching the statistical significance level was detected in the SLEDAI-2K score with the administration of biosimilar RTX. It has also been observed that there was a statistically significant decrease between the SLEDAI-2K scores of originator RTX in the third month and the SLEDAI-2K score assessed three months after the administration of biosimilar RTX and that no efficacy loss was experienced. Therefore, it was concluded that no efficacy loss was monitored after switching originator RTX to biosimilar RTX.

In a study[4] that evaluated originator RTX in patients with moderately-to-severely active SLE, any infusion-related side effect was encountered with a rate of 43.8% in the originator RTX group, and this result was similar to our study. In another study[7], 10/136 (7.3%) patients were detected with mild-to-moderate infusion reaction (hypotension, hypertension, fever, rash), whereas allergic reaction (urticaria) with originator RTX was observed at a rate of 4.5% in our study. Infection-related side effects developed with originator RTX at a rate of 45.5% in our study, whereas any infection, grade 3 and higher infection, and infection-related serious side effect developed in 84.9%, 16.4%, and 19.2% of the patients in another study[5], respectively. In the same study, the most frequently observed infection was upper respiratory tract infection (28.8%). In our study, the most common infection that developed with originator RTX was urinary tract infection, with a rate of 22.7%. In a study[19], the frequencies of infection and severe infection that developed with biosimilar RTX were 18.8% and 9.4%, respectively. In our study, the frequency of infection that developed with biosimilar RTX was 45.5%. The frequency of side effects due to infectious processes was ascertained to be high despite the short follow-up duration under treatment with biosimilar RTX since the process of switching to biosimilar therapy coincided with the COVID-19 pandemic period. There were 18.2% of patients who had a history of infection that required hospitalization with both originator and biosimilar RTX. The different rates of side effects have been encountered in the literature[4,5,7,15].

Limitations of the Study

There were some limitations to our study, which presented single-center real-life data. The number of patients was low, and the study was retrospective. The follow-up period after switching to biosimilar RTX was shorter. No control group was present since the study design compared the periods prior to and after switching therapy in the same patient group. The other important limitation was that the time interval of switching coincided with the whole COVID-19 pandemic period. The majority of these patients were stable and not in flare during the efficacy evaluation. Nevertheless, the medication maintained its effectiveness even after switching from the original RTX to the biosimilar. Despite these limitations, our study is important by presenting beneficial outcomes in the light of real-life data because switching to biosimilar RTX was evaluated in the same homogeneous patient group based on efficacy and safety data as well as the effective factors on the development of side effects were analyzed in a disease which can influence all organs and systems with a severe involvement and may threaten life such as SLE.

Conclusions

Our study demonstrated that no efficacy loss was experienced according to SLEDAI-2K scores after switching to the CT-P10 molecule, which is a biosimilar RTX. In addition, although an increase was encountered in the side effect frequency after switching to biosimilar RTX, it is predicted that switching to biosimilar therapy will create no safety issues since this increase coincided with the COVID-19 pandemic period. Although we have reached this conclusion, further studies with a larger sampling size are needed.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethics Approval

Ethical approval (No. 2023-5/9) was obtained on the 7th March of 2023 from Uludağ University Faculty of Medicine Clinical Research Ethics Committee, Bursa, Turkey. The Uludağ University Faculty of Medicine Clinical Research Ethics Committee also approved the publication of data generated from this study. The study was conducted following the Helsinki Declaration.

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Availability of Data and Materials
The original contribution presented in this study is included in the article. Further inquiries can be directed to the corresponding author by e-mail.

Informed Consent
Informed consent was obtained from all subjects involved in the study.

Authors' Contributions
A. Ekin, S. Mısırcı, B. N. Coşkun, B. Yağız, E. Dalkılıç, Y. Pehlivan. A. Ekin is the owner of the research topic and organized the research team. A. Ekin, B. N. Coşkun, S. Mısırcı were responsible for the writing of the article and reached the patients' data. A. Ekin, Y. Pehlivan, B. Yağız were responsible for the statistics of the study. A. Ekin, E. Dalkılıç, B. Yağız and S. Mısırcı reviewed the literature. Y. Pehlivan and E. Dalkılıç designed the study and analyzed the data.

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