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OPINION REVIEW

Stepanova N. Probiotic interventions in peritoneal dialysis: A review of underlying mechanisms and therapeutic potentials. *World J Nephrol* 2024; 13(4): 98719 [DOI: [10.5527/wjn.v13.i4.98719](https://doi.org/10.5527/wjn.v13.i4.98719)]

REVIEW

Salvadori M, Rosso G. What is new in the pathogenesis and treatment of IgA glomerulonephritis. *World J Nephrol* 2024; 13(4): 98709 [DOI: [10.5527/wjn.v13.i4.98709](https://doi.org/10.5527/wjn.v13.i4.98709)]

Araji G, Keesari PR, Chowdhry V, Valsechi-Diaz J, Afif S, Diab W, El-Sayegh S. Vitamin B12 deficiency in dialysis patients: risk factors, diagnosis, complications, and treatment: A comprehensive review. *World J Nephrol* 2024; 13(4): 100268 [DOI: [10.5527/wjn.v13.i4.100268](https://doi.org/10.5527/wjn.v13.i4.100268)]

MINIREVIEWS

Elahi T, Ahmed S, Mubarak M. Relationship of lupus nephritis and pregnancy: A narrative review. *World J Nephrol* 2024; 13(4): 99700 [DOI: [10.5527/wjn.v13.i4.99700](https://doi.org/10.5527/wjn.v13.i4.99700)]

Deodhare KG, Pathak N. Hypertension and associated complications in pregnant women with chronic kidney disease. *World J Nephrol* 2024; 13(4): 100680 [DOI: [10.5527/wjn.v13.i4.100680](https://doi.org/10.5527/wjn.v13.i4.100680)]

ORIGINAL ARTICLE**Retrospective Cohort Study**

Elahi T, Ahmed S, Mubarak M. Short-term renal and patient outcomes of primary immunoglobulin-associated mesangiocapillary glomerulonephritis: Insights from a developing country. *World J Nephrol* 2024; 13(4): 98969 [DOI: [10.5527/wjn.v13.i4.98969](https://doi.org/10.5527/wjn.v13.i4.98969)]

Shakeel S, Rashid R, Jafry NH, Mubarak M. Adult minimal change disease: Clinicopathologic characteristics, treatment response and outcome at a single center in Pakistan. *World J Nephrol* 2024; 13(4): 99643 [DOI: [10.5527/wjn.v13.i4.99643](https://doi.org/10.5527/wjn.v13.i4.99643)]

Retrospective Study

Kalashnikova E, Isupova E, Gaidar E, Lubimova N, Sorokina L, Chikova I, Kaneva M, Raupov R, Kalashnikova O, Aliev D, Gaydukova I, Kostik M. Outcomes of a 12-month course of early and late rituximab BCD020 biosimilar administration in juvenile systemic lupus erythematosus: A retrospective study. *World J Nephrol* 2024; 13(4): 98393 [DOI: [10.5527/wjn.v13.i4.98393](https://doi.org/10.5527/wjn.v13.i4.98393)]

Puspitasari M, Wardhani Y, Sattwika PD, Wijaya W. Patterns of kidney diseases diagnosed by kidney biopsy and the impact of the COVID-19 pandemic in Yogyakarta, Indonesia: A single-center study. *World J Nephrol* 2024; 13(4): 100087 [DOI: [10.5527/wjn.v13.i4.100087](https://doi.org/10.5527/wjn.v13.i4.100087)]

Observational Study

Tran TTT, Ha TK, Phan NM, Le MV, Nguyen TH. Detection of decline in estimated glomerular filtration rate in patients with type 2 diabetes by cystatin C-based equations. *World J Nephrol* 2024; 13(4): 95761 [DOI: [10.5527/wjn.v13.i4.95761](https://doi.org/10.5527/wjn.v13.i4.95761)]

Varatharajan S, Jain V, Pyati AK, Neeradi C, Reddy KS, Pallavali JR, Pandiyaraj IP, Gaur A. Neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and periostin: Novel urinary biomarkers in diabetic nephropathy. *World J Nephrol* 2024; 13(4): 98880 [DOI: [10.5527/wjn.v13.i4.98880](https://doi.org/10.5527/wjn.v13.i4.98880)]

Jafry NH, Sarwar S, Waqar T, Mubarak M. Clinical course and outcome of adult patients with primary focal segmental glomerulosclerosis with kidney function loss on presentation. *World J Nephrol* 2024; 13(4): 98932 [DOI: [10.5527/wjn.v13.i4.98932](https://doi.org/10.5527/wjn.v13.i4.98932)]

ABOUT COVER

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The primary aim of *World Journal of Nephrology* (*WJN*, *World J Nephrol*) is to provide scholars and readers from various fields of nephrology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, *etc.*

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Retrospective Study

Outcomes of a 12-month course of early and late rituximab BCD020 biosimilar administration in juvenile systemic lupus erythematosus: A retrospective study

Elvira Kalashnikova, Eugenia Isupova, Ekaterina Gaidar, Natalia Lubimova, Lyubov Sorokina, Irina Chikova, Maria Kaneva, Rinat Raupov, Olga Kalashnikova, Damir Aliev, Inna Gaydukova, Mikhail Kostik

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Abstract

BACKGROUND

Juvenile systemic lupus erythematosus (SLE) is a severe, life-threatening disease. However, the role of rituximab in managing juvenile SLE remains undefined, although early biological intervention may improve disease outcomes.

AIM

To assess the differences in the outcomes of different types of rituximab administration (early and late).

METHODS

In this retrospective cohort study, the information of 36 children with SLE with

early (less than 6 months from onset) rituximab administration (ERA), and late (more than 1 year) rituximab administration (LRA) was analyzed. We compared initial disease characteristics at onset, at baseline (start of rituximab), and at the end of the study (EOS) at 12 months, as well as outcomes and treatment characteristics.

RESULTS

The main differences at baseline were a higher daily median dose of corticosteroids, increased MAS frequency, and a higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) in the ERA group. No differences in the main SLE outcomes between groups at the EOS were observed. The part of lupus nephritis patients who achieved remission changed from 44% to 31% in ERA and 32% to 11% in the LRA group. Patients with ERA had a shorter time to achieve low daily corticosteroid dose (≤ 0.2 mg/kg) at 1.2 (0.9; 1.4) years compared to 2.8 (2.3; 4.0) years ($P = 0.000001$) and higher probability to achieve this low dose [hazard ratio (HR) = 57.8 (95% confidence interval (CI): 7.2-463.2), $P = 0.00001$ and remission (SLEDAI = 0); HR = 37.6 (95% CI: 4.45-333.3), $P = 0.00001$]. No differences in adverse events, including severe adverse events, were observed.

CONCLUSION

ERA demonstrated a better steroid-sparing effect and a possibility of earlier remission or low disease activity, except for lupus nephritis. Further investigations are required.

Key Words: Systemic lupus erythematosus; Rituximab; Rituximab BCD020 biosimilar; Anti-CD-20; Biologic; Children

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Core Tip: Systemic lupus erythematosus in children is a severe life-threatening disease that requires systemic immunosuppressive therapy. Early biologic treatment in children with systemic lupus erythematosus can provide faster remission with a better corticosteroid-sparing effect.

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INTRODUCTION

Juvenile systemic lupus erythematosus (SLE) is the most common form of pediatric connective tissue disease, characterized by multi-system involvement and a poor prognosis[1]. In adolescents and young adults, the severity of this condition is linked to an increased risk of complications affecting the kidneys, blood vessels, and central nervous system, along with more significant damage and disease activity. This often requires the use of higher doses of systemic corticosteroids and immunosuppressive agents[2]. Corticosteroids remain the cornerstone of treatment for juvenile SLE with lupus nephritis (LN)[3]. However, the potential toxicity of these drugs and the need for long-term therapy have prompted the development of steroid-sparing strategies[4].

There are no current standardized recommendations for corticosteroid tapering and withdrawal in juvenile SLE, despite the European Alliance of Associations for Rheumatology recommendations to minimize corticosteroid use[5]. The current standard of care therapy (SOCT) involves combinations of corticosteroids, cytotoxic agents, and antimalarials, while the role of biological treatments remains to be fully established. Treatment with cytotoxic agents can result in adverse events affecting the blood, liver, and kidneys, as well as increased risks of fertility issues and cancer in adults[2, 5]. Biological treatments have disease-modifying effects that are similar to or better than SOCT, with fewer adverse events, and may enhance or replace SOCT in certain cases.

Several biologics have been developed for the treatment of SLE: Belimumab, approved for both adults and children; anifrolumab, approved only for adults; and rituximab, which has not yet been approved despite its known clinical efficacy[6-9]. Belimumab is approved for pediatric and adult patients with mild to moderate SLE[6,7]. It acts as a steroid-sparing agent for corticosteroid-dependent patients, particularly those who have previously achieved remission. However, it is unlikely to be effective in patients with highly active SLE[6,7].

Anifrolumab, an anti-interferon drug, may control lupus similarly to non-biological disease-modifying anti-rheumatic drugs, but it is currently only approved for adults. Rituximab is typically used for severe, life-threatening forms of lupus, but has not been officially approved for either adults or children. Despite this, rituximab is included in all current recommendations for lupus treatment in adults and children, though it is usually reserved as a last resort when other treatments have failed[2,4]. Rituximab may be considered in cases of severe lupus with damage to the kidneys, central nervous system, and blood if standard treatments have proven ineffective[2,4].

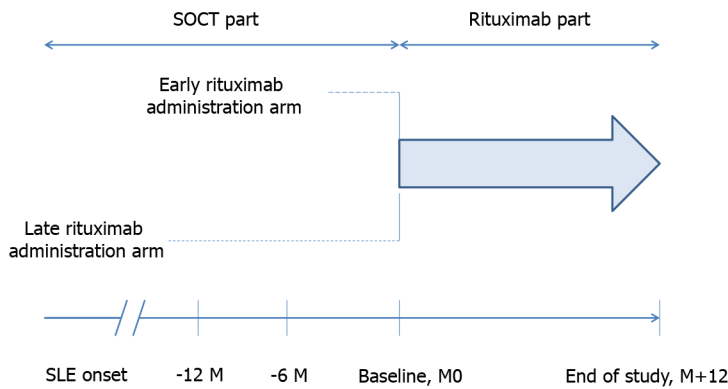


Figure 1 Study flow chart. ERA: Early rituximab administration; LRA: Late rituximab administration.

The question of whether rituximab can be used as a first-line treatment, with or without SOCT, remains open and requires further research[2,4]. Several retrospective studies have failed to demonstrate the benefits of rituximab over traditional non-biologic DMARDs, and no prospective, placebo-controlled trials comparing rituximab with SOCT in children with SLE have been conducted[10,11]. We aimed to compare the outcomes of early *vs* late administration of rituximab.

MATERIALS AND METHODS

Study design

In this retrospective cohort study, we included data on 35 SLE patients (8 boys and 27 girls) from our cohort ($n = 165$, 21.2%), who received rituximab between 2012 and 2022. All included patients failed conventional non-biologic treatment, exhibited high disease activity, or experienced corticosteroid dependence/toxicity. The diagnosis of SLE was confirmed using the Systemic Lupus International Collaborating Clinics classification criteria[12]. The Damage Index was assessed with the Pediatric Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index[13]. LN was diagnosed according to the criteria of the International Society of Nephrology/Renal Pathology Society[14,15].

Rituximab BCD020 biosimilar was prescribed in a dosage of 375 mg/m² every week (2-4 infusions) with repeat courses every 6-12 months (2-4 infusions) depending on disease activity, B-cell depletion, and IgG levels. All patients were divided into two groups: Early Rituximab Administration (ERA), defined as initiation within 6 months from onset; and Late Rituximab Administration (LRA), defined as initiation after more than 1 year. The study flow chart is presented in Figure 1.

Assessment and outcomes

In each patient, we evaluated the dynamics of the following SLE parameters and treatment at three time points: (1) Disease onset; (2) Baseline (start of rituximab); and (3) End of the study (12 months). The parameters assessed included: Demographics, sex and age at onset; disease activity, levels of antinuclear antibodies, antibodies to double-stained deoxyribonucleic acid (dsDNA), C3, C4, hemoglobin, platelets, complete blood count, erythrocyte sedimentation rate, C-reactive protein, urea, creatinine, serum protein and albumin, proteinuria, presence of leukocyturia and hematuria, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[12], Damage Index[13] and LN activity stage[14,15], B-cell level, IgG, and the proportion of patients who achieved SLE remission; concomitant treatment, patients treated with corticosteroids (including median dose), with non-biologic DMARD; and adverse events.

Statistical analysis

The sample size was not calculated initially. Statistical analysis was conducted using STATISTICA software, version 10.0 (StatSoft Inc., Tulsa, OK, United States). Continuous variables were assessed for normality using the Kolmogorov-Smirnov test, which indicated no normal distribution. Continuous variables are presented as median and percentiles (25%; 75%). Categorical variables are presented as proportions. Missing data were neither inputted nor included in the analysis. Pearson's χ^2 test or Fisher's exact test in expected frequencies < 5 was used to compare independent categorical variables. The Mann-Whitney test was employed for continuous variables. Comparison of two dependent quantitative variables was conducted using Wilcoxon's matched pairs test and the McNemar test was applied for dependent categorical variables. A P value < 0.05 was considered statistically significant.

Table 1 Baseline characteristics of systemic lupus erythematosus patients with early and late rituximab administration

Parameter	ERA, n = 16	LRA, n = 19	P value
ANA positivity	15 (94)	13 (68)	0.075
ANA level, titer, Me (25%; 75%)	1280 (1000; 2560)	320 (0; 5120)	0.077
Anti-dsDNA antibodies	9 (56)	12 (63)	0.678
Anti-dsDNA, mU/L, Me (25%; 75%)	19.0 (0; 81)	46 (6; 158)	0.231
Low complement	9/13 (69)	7/11 (64)	0.772
Complement C3, g/L, Me (25%; 75%)	0.57 (0.4; 0.8)	0.85 (0.7; 1.1)	0.059
Complement C4, g/L, Me (25%; 75%)	0.10 (0.06; 0.14)	0.19 (0.10; 0.24)	0.075
Hemoglobin, g/L, Me (25%; 75%)	108 (91; 131)	115 (108; 128)	0.578
Platelets, 10 ⁹ /L, Me (25%; 75%)	270 (140; 305)	246 (193; 273)	0.606
WBC, 10 ⁹ /L, Me (25%; 75%)	8.4 (5.7; 13.5)	5.1 (3.7; 8.3)	0.035
ESR, mm/h, Me (25%; 75%)	13 (5; 22)	12 (6; 22)	0.921
SLEDAI baseline, score, Me (25; 75%)	22 (15; 26)	10 (6; 16)	0.003
SLEDAI baseline, grade			0.074
0 grade	0 (0)	1 (5)	
I grade	0 (0)	3 (16)	
II grade	3 (19)	7 (37)	
III grade	4 (25)	5 (26)	
IV grade	9 (56)	3 (16)	
Damage index, Me (25%; 75%)	1 (0; 1)	1 (0; 1)	0.616
Patients with active lupus nephritis	7 (44)	6 (32)	0.458
Proteinuria, g/24 h, Me (25%; 75%)	1.9 (0.5; 6.0)	0.4 (0; 3.8)	0.463
Urea, mmol/L, Me (25%; 75%)	5.8 (4.9; 8.5)	4.6 (3.7; 5.9)	0.077
Creatinine, mmol/L, Me (25%; 75%)	57 (52; 60)	62 (55; 75)	0.160
Corticosteroids, mg/kg, Me (25%; 75%)	1.0 (0.6; 1.0)	0.3 (0.2; 0.8)	0.027

Data are n (%). ANA: Antinuclear antibodies; dsDNA: Double-stained deoxyribonucleic acid; ERA: Early rituximab administration; ESR: Erythrocyte sedimentation rate; LRA: Late rituximab administration; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; WBC: White blood cells.

RESULTS

Patient characteristics at the disease onset

The studied population consisted of 8 boys (23%) and 27 girls (77%). There were no significant differences between the group with ERA and LRA, except the higher level of SLEDAI in ERA group at 23 (16; 26) compared to LRA at 14 (11; 19) points ($P = 0.012$), and prevalence of the patients with high disease activity (SLEDAI grade IV) (63% *vs* 21%; $P = 0.043$). Patients from the ERA group had a higher frequency of pleurisy (44% *vs* 16%; $P = 0.068$), pericarditis (38% *vs* 11%; $P = 0.058$), ascites (25% *vs* 5%; $P = 0.07$) and macrophage activation syndrome (25% *vs* 5%; $P = 0.096$) with a borderline level of significance.

Baseline patient characteristics

The time before rituximab from SLE onset was different between groups: 3 (2; 6) months in ERA and 22 (14; 36) months ($P = 0.00001$) for LRA. Patients with ERA continued to have higher levels of SLEDAI [22 (15; 26) *vs* 10 (6; 16); $P = 0.003$] and had higher daily median doses of corticosteroids [1.0 (0.6; 1.0) *vs* 0.3 (0.2; 0.8) mg/kg; $P = 0.027$], and WBC levels [8.4 (5.7; 13.5) $\times 10^9$ /L *vs* 5.1 (3.7; 8.3) $\times 10^9$ /L; $P = 0.035$]. Also, patients from the ERA group had higher ANA positivity (94% *vs* 68%; $P = 0.075$), ANA titer [1280 (1000; 2560) *vs* 320 (0; 5120); $P = 0.077$]; lower C3 [0.57 (0.4; 0.8) g/L *vs* 0.85 (0.7; 1.1) g/L; $P = 0.059$]; and C4 fractions of complements [0.10 (0.06; 0.14) g/L *vs* 0.19 (0.10; 0.24) g/L; $P = 0.075$] with borderline significance. There were no differences in the proportion of LN patients and non-biologic DMARD treatment. The baseline characteristics in both groups are presented in Table 1.

Characteristics of patients at the end of the study

There were significant differences in the main outcomes in both groups after 12 months of treatment, except for the higher level of platelets in the group with ERA (Figure 2). A higher frequency of patients with active LN in the ERA group (31% vs 11%) was observed, but the data were non-significant ($P = 0.150$). The part of patients with LN remission decreased from 44% to 31% in the ERA group and from 32% to 11% in the LRA group. Patients with ERA had a shorter time to achieve low daily corticosteroid dose (≤ 0.2 mg/kg): 1.2 (0.9; 1.4) years compared to 2.8 (2.3; 4.0) years ($P = 0.000001$); higher probability to achieve this low dose [LogRank test $P = 0.00015$; hazard ratio (HR) = 57.8 (95%CI: 7.2-463.2), $P = 0.00001$]; and higher probability to achieve the remission [SLEDAI = 0; LogRank test $P = 0.021$; HR = 37.6 (95%CI: 4.45-333.3), $P = 0.00001$]. The data are presented in Table 2 and Figure 3.

Safety of rituximab treatment

During the 12-month rituximab course, no differences in severe adverse events were observed. Nearly half of the patients of both groups received co-trimoxazol prophylaxis. The IgG level was similar in both groups, but patients with ERA frequently had low IgG levels (< 4.5 g/L) and a higher proportion of ERA patients had B-cell depletion. The number of patients who received replacement IVIG treatment was equal in both groups.

DISCUSSION

In this small study, differences in outcomes between early and LRA for the treatment of juvenile SLE were observed. Patients who received early rituximab had the potential for faster tapering of systemic corticosteroids and more rapid achievement of SLE remission, except for those with LN.

The role of rituximab in SLE has not yet been fully established, despite its known efficacy. It is typically used as a treatment for resistant disease or as a new treatment for severe, life-threatening courses of the disease[15]. Rituximab's effectiveness was demonstrated in a large meta-analysis of 35 uncontrolled studies and case reports, in which 91% of the 188 patients showed significant improvement in at least one systemic SLE manifestation[15]. Many uncontrolled trials and case reports have highlighted rituximab's effectiveness, whereas randomized controlled trials, such as EXPLORER and LUNAR, which did not achieve their primary endpoints[16,17]. However, both trials demonstrated effectiveness compared to a placebo[16,17]. Rituximab is recommended to reduce disease activity, serum levels, proteinuria, and the need for corticosteroids[18]. According to these studies, rituximab is more effective as an adjuvant therapy to control severe manifestations of SLE rather than as an induction therapy[19]. Rituximab has not yet been approved by the Food and Drug Administration for the treatment of SLE in the United States.

The steroid-sparing effect of rituximab has been demonstrated in most pediatric and adult studies of SLE, similar to our findings, with a greater potential to reduce corticosteroid use when rituximab is administered early[1,11,19,20]. Corticosteroids, the cornerstone of SLE treatment, are associated with significant damage due to their toxicity (osteoporosis, avascular necrosis, cataract, steroid diabetes, striae, hypertension, *etc.*)[21]. Adults with childhood SLE onset had significantly higher corticosteroid-induced damage compared to those with disease onset after 18 years (odds ratio = 1.7, 95%CI: 1.1-2.8)[22]. Pediatric SLE patients with short stature (23%) had higher cumulative corticosteroid dosage[23]. Delayed puberty, caused by corticosteroids, occurred in 15% of females and 24% of males[24]. Transitioning from oral to intravenous corticosteroids may reduce associated side effects and lower the cumulative oral corticosteroid dose while maintaining efficacy. Repeated IV usage of corticosteroids improved outcomes in LN and helps to reduce the dose of oral corticosteroids[25]. Low dose intravenous corticosteroid therapy is effective as high dose in patients with LN with fewer corticosteroid-associated side effects[26]. The potential for achieving remission more rapidly with lower corticosteroid burden may improve the disease outcomes with less damage and higher quality of life.

Contemporary guidelines for pediatric and adult SLE recommend minimizing corticosteroid use whenever possible[4, 27]. Early administration of rituximab appears to be a promising strategy to achieve this goal. Long-term rituximab therapy has demonstrated a higher relapse-free survival rate in adult SLE patients compared to standard conventional treatment[28].

Lower IgG levels and a higher proportion of patients with B-cells were observed in the ERA group, compared to the LRA group. This may be attributed to the fact that patients in the ERA group received more treatment agents simultaneously, which might contribute to a cumulative effect of combined therapies with different targets. Fortunately, this lower IgG level did not lead to increased frequency or severity of infections that was demonstrated earlier[29,30].

A recent study from India suggested that rituximab was an effective (decreased SLEDAI, corticosteroids, and proteinuria, and no flares in 82% of children for 24 months) and safe treatment for pediatric SLE in a country with a very high burden of infectious diseases[31]. Early-onset SLE is significant because juvenile SLE is associated with higher disease activity, a greater medication burden, and an increased risk of internal organ damage compared to adult-onset SLE[32-34]. In a multivariate model adjusted for age, disease duration, and other clinical characteristics, juvenile SLE was independently associated with an increased risk of death (HR = 3.1, 95%CI: 1.3-7.3)[35]. Survival rates for children with juvenile SLE (mean age of 11.6 ± 2.6 years) are 88% at 2 years, 76% at 5 years, and 64% at 10 years after diagnosis[36]. Irreversible organ damage develops in 44.2% of children with juvenile SLE, occurring only 3.8 years after diagnosis. This suggests a high risk of comorbidity accumulation at a young age in these adults[37].

The same immunosuppressive drugs are used to treat both juvenile and adult SLE. Hydroxychloroquine is prescribed to all patients with adult and juvenile SLE who have no contraindications to its use[4]. Along with hydroxychloroquine, GCs are the mainstay of treatment for adult SLE patients because of their anti-inflammatory and immunosuppressive effects[38]. However, prolonged use of glucocorticoids leads to numerous side effects, including an increased risk of

Table 2 Characteristics of systemic lupus erythematosus patients with early and late rituximab administration at the end of the study

Parameter	ERA, n = 16	LRA, n = 19	P value
ANA positivity	10 (63)	10 (53)	0.557
ANA level, titer, Me (25%; 75%)	320 (160; 3200)	400 (80; 2560)	0.620
Anti-dsDNA antibodies	1 (6)	5 (26)	0.112
Anti-dsDNA, mU/L, Me (25%; 75%)	5.3 (0; 12)	9 (0; 21)	0.451
Low complement	2/10 (20.0)	3/11 (27.3)	0.696
Complement C3, g/L, Me (25%; 75%)	0.91 (0.7; 1.2)	1.22 (0.9; 1.3)	0.185
Complement C4, g/L, Me (25%; 75%)	0.18 (0.1; 0.3)	0.19 (0.1; 0.3)	0.961
Hemoglobin, g/L, Me (25%; 75%)	133 (130; 139)	130 (110; 134)	0.092
Platelets, 10 ⁹ /L, Me (25%; 75%)	294 (267; 319)	232 (212; 260)	0.004
WBC, 10 ⁹ /L, Me (25%; 75%)	5.1 (4.5; 6.8)	5.2 (3.9; 6.1)	0.659
ESR, mm/h, Me (25%; 75%)	3 (2; 20)	7 (2; 16)	0.535
SLEDAI, score, Me (25; 75%)	2 (0; 4)	2 (0; 6)	1.0
SLEDAI score, grade			0.571
0 grade	5 (31)	7 (37)	
I grade	9 (56)	7 (37)	
II grade	2 (13)	4 (21)	
III grade	0 (0)	0 (0)	
IV grade	0 (0)	1 (5)	
Damage index	1 (0; 1)	1 (0; 2)	0.874
Patients with active lupus nephritis	4/13 (31)	2 (11)	0.150
Proteinuria, g/24 h, Me (25%; 75%)	0.3 (0; 0.4)	0.07 (0;0.17)	0.427
Urea, mmol/L, Me (25%; 75%)	3.7 (3.0; 4.6)	3.7 (3.2; 4.7)	0.605
Creatinine, mmol/L, Me (25%; 75%)	57 (54; 67)	63 (58; 67)	0.187
Corticosteroids, mg/kg, Me (25%; 75%)	0.1 (0.08; 0.16)	0.1 (0.06; 0.2)	0.842
Patients with prednisolone ≤ 0.2 mg/kg	14 (88)	17 (90)	0.855
Time to prednisolone ≤ 0.2 mg/kg, years, Me (25%; 75%)	1.2 (0.9; 1.4)	2.8 (2.3; 4.0)	0.000001
Safety			
Adverse events			0.707
Not reported	13 (82)	16 (84)	
Serious adverse events	1 (6)	2 (11)	
Frequent respiratory infections	1 (6)	0 (0)	
Focal infections	1 (6)	1 (5)	
Co-trimoxazol prophylaxis	9 (56)	9 (47)	0.716
Ig G level, g/L, Me (25%; 75%)	9.3 (4.1; 9.7)	8.3 (6.4;12.3)	0.676
Low Immunoglobulin	9/11 (82)	7/10 (70)	0.034
B-lymphocytes depletion	10/10 (100)	5/8 (63)	0.034
Intravenous immunoglobulin	8 (50)	7 (37)	0.433

Data are n (%). ANA: Antinuclear antibodies; dsDNA: Double-stained deoxyribonucleic acid; ERA: Early rituximab administration; ESR: Erythrocyte sedimentation rate; LRA: Late rituximab administration; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; WBC: White blood cells.

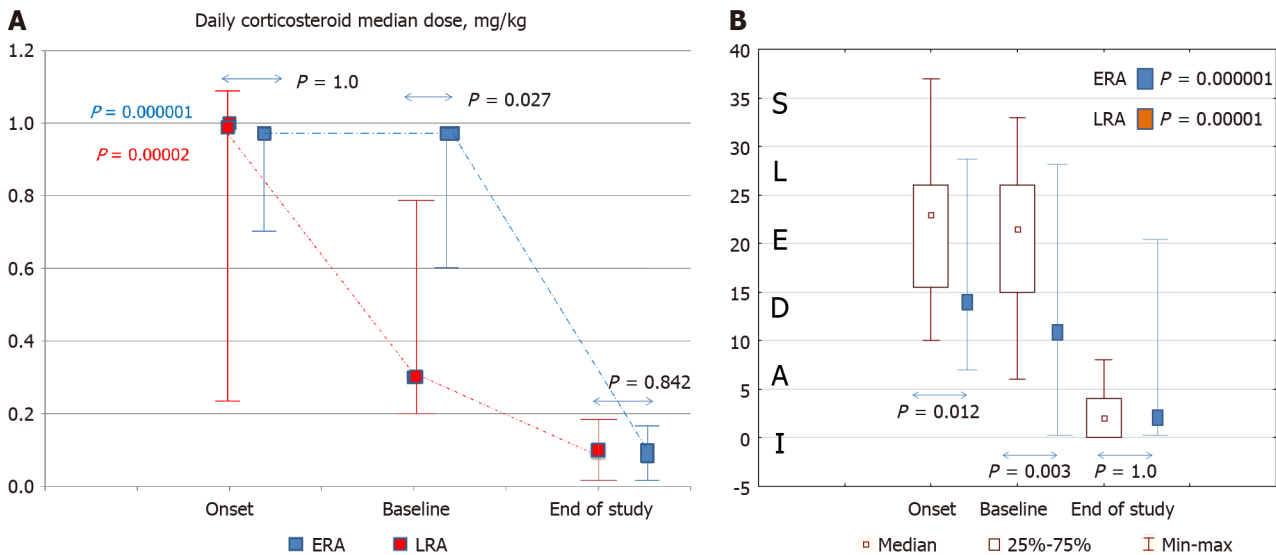


Figure 2 Outcomes after 12 months of treatment with early and late administration of rituximab BCD020 biosimilar. A: Dynamics of corticosteroids; B: Dynamics of Systemic Lupus Erythematosus Disease Activity Index. ERA: Early rituximab administration; LRA: Late rituximab administration.

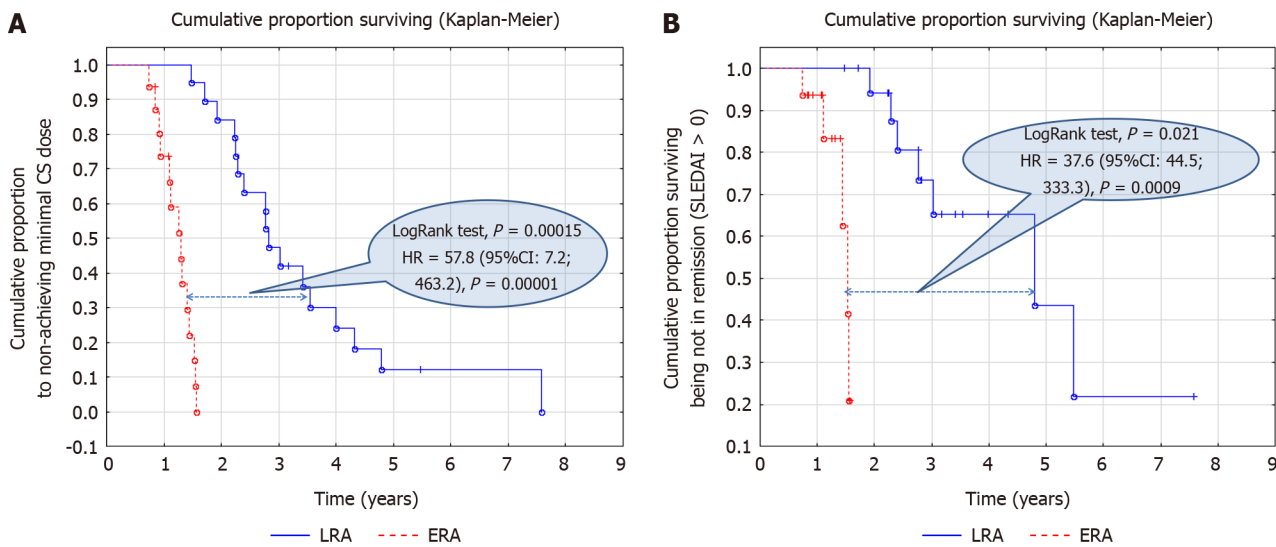


Figure 3 Long-lasting treatment outcomes of rituximab BCD020 biosimilar with early and late administration. A: Probability of achieving low (≤ 0.2 mg/kg) corticosteroid dose in systemic lupus erythematosus patients with early and late rituximab administration; B: Probability of achieving remission (Systemic Lupus Erythematosus Disease Activity Index = 0) in systemic lupus erythematosus patients with early rituximab administration (ERA) and late rituximab administration (LRA).

infections, metabolic disorders, cardiovascular disease, and irreversible organ damage[38]. Non-biologic disease-modifying drugs are prescribed less frequently in adult SLE patients compared to children[35]. Mycophenolate mofetil, cyclophosphamide, and azathioprine are the primary drugs used to treat LN in both adults and children with SLE[4].

Regarding biologic agents, belimumab or anifrolumab is recommended for patients who do not respond to hydroxychloroquine monotherapy, or to hydroxychloroquine in combination with glucocorticoids and/or other immunosuppressive drugs, or for patients who cannot reduce the dose of glucocorticoids below to acceptable levels for continuous use. The use of rituximab may be considered in severe, organ-threatening, refractory disease[4].

Due to the severity of SLE in children, they often receive higher doses of corticosteroids and cyclophosphamide. This can lead to over-treatment, as physicians are often concerned about the disease and its potential complications. Consequently, pediatric SLE patients may suffer more from treatment-related damage than disease-related damage. Early use of biologics in the treatment of juvenile SLE could improve this situation and reduce the need for corticosteroids and cyclophosphamide with better outcomes.

CONCLUSION

This study showed that ERA offers a better steroid-sparing effect and the possibility of earlier remission or lower disease activity, except in patients with LN. No significant differences were found in severe adverse events between the ERA and LRA groups, and further research is needed.

FOOTNOTES

Author contributions: Kostik MM, Kalashnikova EM, and Kalashnikova LS contributed to conceptualization of the study, and writing, review and editing of the manuscript; Kostik MM and Chikova IA contributed to the methodology; Aliev DB and Gaydukova IZ contributed software and resources, and contributed to the data curation; Kalashnikova OV, Isupova EA, Gaidar EV, and Kaneva MA contributed to the data validation; Lubimova NA and Raupov RK contributed to the formal data analysis; Sorokina LS contributed to the overall investigation and the data visualization; Kostik MM contributed to writing in original draft preparation of the manuscript, and provided funding, supervision, and project administration; All authors have read and agreed to the published version of the manuscript.

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