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ORIGINAL ARTICLE

COVID-19 in Systemic Lupus Erythematosus patients treated with belimumab: a retrospective clinical study

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Abstract

Background Routine use of immunosuppressive agents in systemic lupus erythematosus (SLE) patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) potentially increases the risk of adverse outcomes. belimumab, a monoclonal antibody for the treatment of SLE, remains untested for its specific impact on coronavirus disease 2019 (COVID-19) symptoms in these patients. Here, this research investigated the effect of belimumab on COVID-19 symptoms in SLE patients infected with SARS-CoV-2.

Methods This study enrolled SLE patients who underwent treatment with belimumab. After thorough screening based on the inclusion and exclusion criteria, data pertaining to COVID-19 for both the participants and their cohabitants were obtained through telephone follow-up. The potential impact of belimumab on COVID-19 was evaluated by comparing COVID-19 symptoms and medication use across various groups to investigate the association between belimumab treatment and COVID-19 in SLE.

Results This study involved 123 SLE patients, of whom 89.4% tested positive for SARS-CoV-2. Among cohabitants of SLE patients, the SARS-CoV-2 positive rate was 87.2% ($p = 0.543$). Patients treated with belimumab exhibited a lower incidence of multiple COVID-19 symptoms than their cohabitating counterparts ($p < 0.001$). This protective effect was found to be partially related to the time of last belimumab administration. Among those with COVID-19, 30 patients opted to discontinue their anti-SLE drugs, and among them, 53% chose to discontinue belimumab. Discontinuing drugs did not increase the risk of hospitalization due to SARS-CoV-2 infection.

Conclusion This study concluded that treatment with belimumab did not increase susceptibility to COVID-19 and beneficially alleviated the symptoms of COVID-19.

Keywords Systemic Lupus Erythematosus (SLE) · Coronavirus disease 2019 (COVID-19) · Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) · Belimumab · Retrospective clinical study

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), which led to a pandemic that posed a serious threat to human health and imposed a considerable medical burden [1]. As of 10 March 2023, there have been more than 670 million confirmed cases and 681,955 deaths worldwide [2]. The primary clinical manifestations of COVID-19 include fever, cough, weakness, dyspnoea, myalgia, expectoration, vomiting, and diarrhoea [3, 4], and fatalities often show intravascular immune thrombosis, especially of the microvasculature [5, 6].

Systemic lupus erythematosus (SLE) is a disease in which the immune system attacks healthy cells and tissues throughout the body. Immune system activation in SLE is characterized by interferon-driven, excessive B- and T-cell responses and loss of immune tolerance to self-antigens [7]. When infected with SARS-CoV-2, immune dysfunction, the routine use of immunosuppressive drugs, and multisystem damage in renal and haematological diseases put patients with SLE at increased risk for multiple adverse outcomes [8–10]. Therefore, medicines may have to be rebalanced in SLE patients with COVID-19. At present, the recommended therapeutic drugs for SLE include hydroxychloroquine, traditional disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and targeted biological agents [11]. Among them, belimumab, a fully humanized monoclonal antibody against B lymphocyte stimulator (BLyS) [12], is widely used to treat seropositive SLE. Previous studies have shown that it significantly reduces the activity of the disease and improves the quality of life of patients [13, 14]. However, it is still unknown whether the use of belimumab has a protective effect or aggravates SLE during SARS-CoV-2 infection.

This study involved a cohort of SLE patients treated with belimumab to analyse their infection and SLE disease status during COVID-19. The results can help clinicians and public health care managers make decisions about preventive measures and treatment in this patient group.

Methods

Study design

This retrospective study was approved by the Biomedical Ethics Committee of West China Hospital, Sichuan University. The approval number assigned to this study is 2023 (277). This study included patients who sought medical care at the Department of Rheumatology and Immunology, West China Hospital, Sichuan University, China, from January 30, 2020, to January 30, 2023. Screening of potential participants was conducted based on the following inclusion criteria: (1) age range of 18 to 80 years; (2) diagnosis of SLE according to either the 1997 American College of Rheumatology criteria or the 2012 Systemic Lupus International Collaborating Clinics criteria; and (3) initiation of belimumab treatment at least 3 months prior to SARS-CoV-2 infection. The exclusion criteria were as follows: (1) diagnosis of malignancy; (2) pregnancy during the COVID-19 period; and (3) presence of further infectious diseases, such as HIV or hepatitis B. SARS-CoV-2 infection was diagnosed by a positive test for either SARS-CoV-2 RNA or antigen. Individuals who resided with an SLE patient and shared living quarters one month prior to and following SARS-CoV-2 infection were defined as “cohabitants”. In this study, the comparison of SLE patients with their cohabitants may reduce the bias caused by living environment, economic situation and medical conditions to some extent. These definitions accurately classified the participants and maintained the integrity of this study.

Data collection for this study involved obtaining the following information from participants:

1. **Basic information**: age, sex, body mass index (BMI), living environment, smoking status, and education level.
2. **SLE disease status and drug information**: duration of SLE disease course, organs/systems involved in SLE, anti-SLE drugs used, dose of glucocorticoids administered, duration and protocol of belimumab use, and interval between last use of belimumab and SARS-CoV-2 infection.
3. **COVID-19-related information**: SARS-CoV-2 infection status, symptoms experienced during SARS-CoV-2 infection, types of drug discontinuation, timing and duration of drug discontinuation, and whether the individuals was admitted to a hospital.
4. **Cohabitant information**: SARS-CoV-2 infection status and symptoms experienced by those individuals residing with SLE patients.

The specific data collection content and definition criteria are detailed in the standardized questionnaire form (Supplement 1).

Statistical analysis

GraphPad Prism 8 was used for data analysis in this study. Categorical variables were described as frequencies (percentages), and differences were assessed with the use of Fisher’s exact test or Pearson’s chi-square test. Continuous

variables were expressed as the interquartile range (IQR) or mean ± standard deviation (SD) according to the normality of their distribution and compared using the Mann–Whitney test or Student's t test, respectively. The Kruskal–WallisU test was applied to compare continuous variables across three groups defined by the interval between last belimumab use (< 1 month, 1–3 months, and > 3 months) in cases where data did not exhibit a normal distribution. The p value < 0.05 was considered statistically significant.

Result

A total of 123 participants, all diagnosed with SLE and treated with belimumab, were included in this follow-up study. 85% of the participants were women, with a mean age of 36 years and a mean duration of SLE of 5.9 years. Of these, 110 individuals (89.4%) were infected with SARS-CoV-2 during the survey period. Among the 227 cohabitants, 198 (87.2%) were positive for SARS-CoV-2. Notably, no deaths were reported during the study period, although one SLE patient required hospitalization due to COVID-19.

COVID-19 status in SLE patients treated with belimumab

Of the 123 SLE patients treated with belimumab, 110 were positive for COVID-19. Notably, none of the patients were hospitalized for SLE exacerbation during COVID-19, and only one patient was hospitalized for severe COVID-19. SARS-CoV-2-positive and SARS-CoV-2-negative patients were similar in terms of age, sex, BMI and education level. There were no significant differences in disease-related organ/system involvement or medication regimen (Table 1). Interestingly, compared to subjects without COVID-19, a

Table 1 Basic information in SLE patients treated with Belimumab

	SARS-CoV-2 negative	SARS-CoV-2 positive	p Value
	n = 13	**n = 110**	
Basic information			
Male, n (%)	3(23)	16(15)	0.421
Age, Mean ± SD, years	40.08 ± 15.3	35.65 ± 15.1	0.320
BMI, Mean ± SD, kg/m2	20.35 ± 1.912	22.08 ± 3.121	0.056
Living environment, urban areas, n (%)	8(62)	96(87)	0.015
Smoke, n (%)	0(0)	6(5)	0.388
Degree of education			0.447
Primary school, n (%)	4(30)	15(14)	
Junior high school, n (%)	3(23)	30(27)	
Senior high school/Technical secondary school, n (%)	2(15)	19(17)	
Bachelor/Junior college, n (%)	4(30)	46(42)	
Vaccination status, n (%)	4(31)	38(35)	0.786
Number of vaccinations administered, Mean ± SD, times	0.8364 ± 1.223	0.7692 ± 1.235	0.852
SLE disease and drug			
Disease course, Mean ± SD, years	7.231 ± 6.234	5.782 ± 5.299	0.362
Damaged organs/systems			
Arthrosis, n (%)	0(0)	7(6)	0.349
Kidney, n (%)	9(69)	81(74)	0.735
Skin, n (%)	0(0)	4(4)	0.485
Hematologic system, n (%)	5(38)	34(31)	0.580
Traditional therapeutic drugs			
DMARDs, n (%)	8(62)	67(61)	0.965
Glucocorticoids, n (%)	11(85)	103(94)	0.238
Aspirin, n (%)	2(15)	5(5)	0.111
Anticoagulant drugs, n (%)	0(0)	2(2)	0.624
Dose of glucocorticoids			0.629
Low dose, n (%)	7(54)	68(62)	
Medium dose, n (%)	5(38)	36(33)	
High dose, n (%)	0(0)	0(0)	-
Duration of belimumab use, Mean ± SD, years	1.1 ± 0.8073	0.9186 ± 0.5193	0.267
Protocol of belimumab use, IQR, mg/per month	240.00, 510.00	480.00, 480.00	0.117

Abbreviations: SLE, systemic lupus erythematosus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BMI, body mass index; DMARDs, traditional disease-modifying anti-rheumatic drugs

higher proportion of SARS-CoV-2-positive patients lived in towns (62% vs. 87%, $p = 0.015$).

COVID-19 symptoms in SLE patients using belimumab and their cohabitants

Given the above results, which suggest that residential environment may affect the acquisition of COVID-19 in patients, this study next compared patients with SARS-CoV-2-positive SLE with their cohabitants in an attempt to reduce some individual bias due to residential location. There was no significant difference in the SARS-CoV-2 positivity rate between the two groups (89.4% vs. 87.2%, $p = 0.543$). Notably, significant differences were observed for various COVID-19 symptoms. When compared with their cohabitants, belimumab-treated individuals were more likely to be asymptomatic (10% vs. 1%, $p < 0.001$) and less likely to have fever (44% vs. 84%, $p < 0.001$), cough (74% vs. 95%, $p < 0.001$), expectoration (66% vs. 91%, $p < 0.001$), sore throat (44% vs. 79%, $p < 0.001$), myalgia (21% vs. 65%, $p < 0.001$), weakness (28% vs. 48%, $p < 0.001$), and taste/olfactory changes (25% vs. 44%, $p < 0.001$). Moreover, the belimumab group exhibited a lower likelihood of developing febrile symptoms, a shorter duration of fever (1.33 vs. 1.63, $p = 0.004$), and a lower maximum body temperature ($p = 0.005$) (Table 2).

COVID-19 symptoms at various intervals after last belimumab application

To explore the potential association between the interval of last belimumab application and COVID-19, subjects were divided into three groups according to the interval from the last belimumab application to SARS-CoV-2 infection (less than 1 month, 1–3 months, and more than 3 months) (Table 3). After matching for sex, age, total duration of belimumab administration, and medication regimen, the results suggested that the main manifestations of COVID-19 in individuals who used belimumab within 1 month were low-grade fever (73%) and upper respiratory symptoms such as expectoration (76%) and sore throat (61%). In the cohort who used belimumab within 1 to 3 months, moderate fever was the most common. Those who were last treated with belimumab more than 3 months ago were likely to have high fever (42%) and vomiting (17%) but the lowest rates of upper respiratory symptoms among the three groups.

The impact of the withdrawal of anti-SLE drugs on COVID-19

When SLE patients are infected with SARS-CoV-2, some choose to discontinue some or all medicines. In the study cohort, decisions to discontinue anti-SLE drugs were observed in 30 patients with SLE, with belimumab (53%) being the most frequently discontinued medication during SARS-CoV-2 infection (Fig. 1A). The majority of these patients were infected within 3 months (54%) after their

Table 2 COVID-19 status in SLE patients using Belimumab and their cohabitants

	Users of Belimumab	Cohabitants	*p* Value
	n = 110	n = 198	
SARS-CoV-2 positive cases, positive/total cases, n/n	110/123	198/227	0.543
COVID-19 related symptoms			
Asymptomatic, n (%)	10(10)	1(1)	< 0.001
Fever, n (%)	48(44)	167(84)	< 0.001
Days of fever, Mean ± SD, days	1.333 ± 0.6030	1.638 ± 0.6169	0.004
Maximum body temperature			0.005
Low fever, n (%)	22(46)	24(14)	
Moderate fever, n (%)	18(38)	128(77)	
High fever, n (%)	8(17)	15(9)	
Cough, n (%)	81(74)	188(95)	< 0.001
Expectoration, n (%)	73(66)	181(91)	< 0.001
Sore throat, n (%)	48(44)	157(79)	< 0.001
Dyspnea, n (%)	1(1)	8(4)	0.089
Diarrhea, n (%)	10(10)	12(6)	0.476
Vomiting, n (%)	8(7)	9(5)	0.446
Myalgia, n (%)	23(21)	129(65)	< 0.001
Weakness, n (%)	31(28)	95(48)	< 0.001
Taste/smell changes, n (%)	27(25)	87(44)	< 0.001

Abbreviations: SLE, systemic lupus erythematosus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019

Table 3 COVID-19 symptoms at different intervals of last Belimumab use

	Less than 1 month	1 to 3 months	More than 3 months	*P* value
	n = 46	n = 35	n = 29	
Basic information				
Male, n (%)	8(17)	6(17)	2(7)	0.396
Age, Mean ± SD, years	34.13 ± 15.75	36.54 ± 14.48	36.97 ± 15.07	0.671
BMI, Mean ± SD, kg/m2	21.58 ± 2.739	22.85 ± 3.654	22.16 ± 3.089	0.246
Living environment, urban areas, n(%)	43(93)	30(86)	23(79)	0.190
Smoke, n (%)	2(4)	3(9)	1(3)	0.608
Education background				0.862
Primary school, n (%)	5(11)	5(14)	5(17)	
Junior high school, n (%)	13(28)	11(31)	6(21)	
Senior high school/Technical secondary school, n (%)	10(22)	5(14)	4(14)	
Bachelor/Junior college, n (%)	18(39)	14(40)	14(48)	
Vaccination status, n (%)	15(33)	14(40)	9(31)	0.707
SLE disease and drug				
Damaged organs/systems				
Arthrosis, n (%)	3(7)	1(3)	3(10)	0.473
Kidney, n (%)	32(70)	28(80)	21(72)	0.564
Hematologic system, n (%)	15(33)	10(29)	9(31)	0.927
Duration of belimumab use, Mean ± SD, years	0.8565 ± 0.4554	1.186 ± 0.6074	0.6948 ± 0.3480	< 0.001
Protocol of belimumab use, IQR, mg/per month	480.00, 510.00	300.00, 480.00	480.00, 600.00	< 0.001
About COVID-19				
COVID-19 related symptoms				
Asymptomatic, n (%)	3(7)	4(11)	2(7)	0.696
Fever, n (%)	20(43)	16(46)	12(41)	0.941
Days of fever, Mean ± SD, days	1.158 ± 0.3746	1.75 ± 0.8563	1.333 ± 0.4924	0.053
Maximum body temperature				0.001
Low fever, n (%)	14(73)	3(19)	5(42)	
Moderate fever, n (%)	5(26)	11(69)	2(17)	
High fever, n (%)	1(5)	2(13)	5(42)	
Cough, n (%)	38(83)	24(69)	19(66)	0.187
Expectoration, n (%)	35(76)	24(69)	14(48)	0.043
Sore throat, n (%)	28(61)	12(34)	8(28)	0.007
Dyspnea, n (%)	0(0)	1(3)	0(0)	0.350
Diarrhea, n (%)	2(4)	4(11)	4(14)	0.323
Vomiting, n (%)	0(0)	3(9)	5(17)	0.019
Myalgia, n (%)	5(11)	9(26)	9(31)	0.079
Weak, n (%)	13(28)	10(29)	8(28)	0.996
Taste/smell changes, n (%)	8(17)	9(26)	9(31)	0.376

Abbreviations: COVID-19, coronavirus disease 2019; BMI, body mass index; SLE, systemic lupus erythematosus

last belimumab treatment (Fig. 1B). Most patients opted to stop the medication on the first day of COVID-19 symptoms (47%), while three patients discontinued their medication prior to the onset of symptoms to avoid potential immune effects of SLE drugs (Fig. 1C). The duration of discontinuation was most frequently within 7 days (40%) or more than 14 days (40%) (Fig. 1D).

This study further investigated the factors that were associated with the discontinuation of belimumab treatment during SARS-CoV-2 infection (Table 4). Among the demographic characteristics of the cohort, a significant difference was observed in the proportion of individuals with higher education levels between those who discontinued treatment and those who did not (67% vs. 33%). Notably, 4 patients with an interval of more than 1 year between the last application of belimumab chose to discontinue the drug during SARS-CoV-2 infection. Patients who discontinued the drug during the infection period were more likely to have fever (63% vs. 35%, $p = 0.008$) and were more frequently associated with cough (97% vs. 65%, $p = 0.001$), expectoration (93% vs. 56%, $p < 0.001$), and weakness (53% vs. 19%, $p < 0.001$). Importantly, none of the patients who discontinued belimumab treatment were hospitalized for SLE exacerbation.

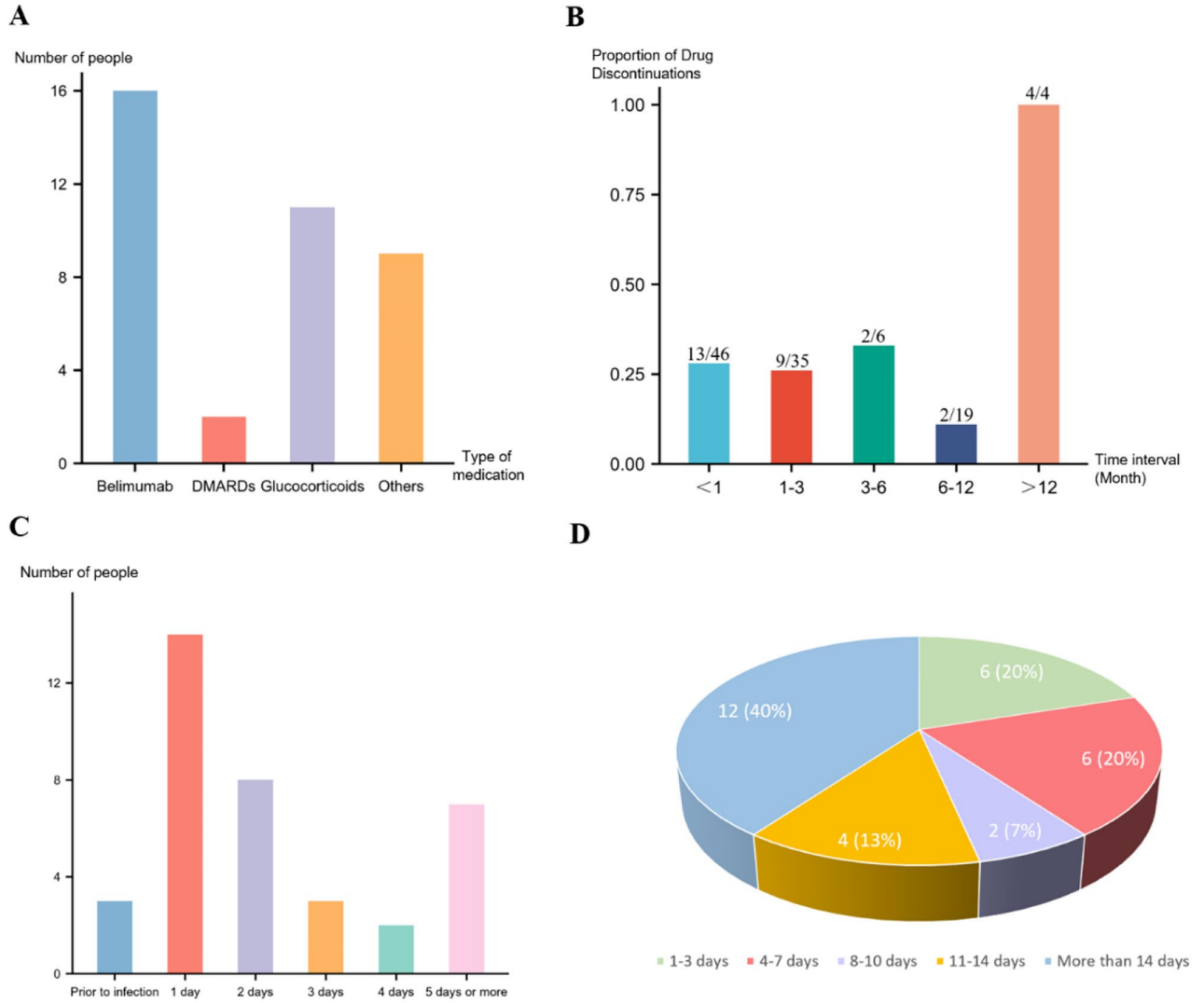

Fig. 1 The impact of withdrawal of anti-SLE drugs in COVID-19. (**A**) The figure illustrates the number of people in our cohort who chose to discontinue different anti-SLE drugs during COVID-19 infection. "Other" includes hydroxychloroquine, calcium tablet, gamma globulin, but not nonsteroidal anti-inflammatory drugs (NSAIDs). Traditional disease-modifying anti-rheumatic drugs, DMARDs; (**B**) Discontinuation rates are shown for patients with different intervals between COVID-19 infection and last belimumab use. The numbers above the bars are the number of discontinuing drugs/total number included in each interval. The abscissa values are in months; (**C**) Bars show the number of patients who discontinued the drug on different days of COVID-19 symptoms; (**D**) Pie charts show the number and proportion of patients with different durations of discontinuation

Discussion

People with autoimmune diseases, such as, such as SLE, are at high risk for severe COVID-19 [15], and the use of immunosuppressive drugs in these populations has been identified as a risk factor for adverse outcomes in multiple studies [16]. belimumab is one of the commonly used biological agents in patients with SLE [17, 18]. In COVID-19, the effects of belimumab on patients' symptoms and drug discontinuation are still unclear. Our results show that the application of belimumab in SLE patients reduced the occurrence of COVID-19-related symptoms. Furthermore, it alleviated disease severity, and the impact of SARS-CoV-2 infection. These findings contribute to bridging the knowledge gap regarding the specific effects of belimumab on SLE patients during COVID-19.

Among SLE patients receiving belimumab, SARS-CoV-2 infection was associated only with the residential environment; a higher proportion of patients infected with SARS-CoV-2 lived in cities. Indeed, living in cities was a risk factor for SARS-CoV-2 infection, independent of patients' basic demographic information, SLE disease course, and other medicines. This is consistent with the SARS-CoV-2 transmission model proposed by Eilersen et al., which

Table 4 The impact of withdrawal of anti-SLE drugs in COVID-19

	Continuing to Take medication	Discontinuing medications	*p* value
	n = 80	n = 30	
Basic information			
Male, n (%)	12(15)	5(17)	0.830
Age, Mean ± SD, years	36.65 ± 15.87	32.97 ± 12.67	0.256
BMI, Mean ± SD, kg/m2	22.3 ± 3.286	21.46 ± 2.574	0.259
Rate of urban areas, n (%)	67(84)	29(97)	0.070
Smoke, n (%)	6(8)	0(0)	0.123
Education background			0.012
Primary school, n (%)	12(15)	3(10)	-
Junior high school, n (%)	25(31)	5(17)	-
Senior high school/Technical secondary school, n (%)	17(21)	2(7)	-
Bachelor/Junior college, n (%)	26(33)	20(67)	-
Vaccination status, n (%)	26(33)	12(40)	0.461
SLE disease and drug			
Disease course, Mean ± SD, years	6.156 ± 5.697	4.783 ± 3.963	0.228
Damaged organs/systems			
Arthrosis, n (%)	6(8)	1(3)	0.425
Kidney, n (%)	61(76)	19(63)	0.176
Skin, n (%)	2(3)	2(7)	0.299
Hematologic system, n (%)	24(30)	9(30)	> 0.9999
Traditional therapeutic drugs			
DMARDs, n (%)	52(65)	15(50)	0.151
Glucocorticoids, n (%)	76(95)	27(90)	0.339
Aspirin, n (%)	5(6)	0(0)	0.161
Anticoagulant drugs, n (%)	2(3)	0(0)	0.382
Dose of glucocorticoids			0.011
Low dose, n (%)	44(56)	23(77)	-
Medium dose, n (%)	32(40)	4(13)	-
High dose, n (%)	0(0)	0(0)	-
Duration of belimumab use, Mean ± SD, years	0.9225 ± 0.5578	0.9083 ± 0.4073	0.899
Protocol of belimumab use, IQR, mg/per month	480.00, 480.00	480.00, 480.00	0.688
Interval between last use of Belimumab and COVID-19 infection			0.924
Less than 1 month, n (%)	33(41)	13(43)	
Within 1 to 3 months, n (%)	26(33)	9(30)	
Within 3 months to 6 months, n (%)	4(5)	2(7)	
Within six months to one year, n (%)	17(21)	2(7)	
More than one year, n (%)	0(0)	4(13)	
About COVID-19			
Vaccination status, n (%)	26(33)	12(40)	0.461
The number of doses of vaccination given, Mean ± SD, times	0.8 ± 1.216	0.9333 ± 1.258	0.613

Table 4 (continued)

	Continuing to Take medication	Discontinuing medications	*p* value
	n = 80	n = 30	
COVID-19 related symptoms			
Asymptomatic, n (%)	9(11)	0(0)	0.055
Fever, n (%)	28(35)	19(63)	0.008
Days of fever, Mean ± SD, days	1.536 ± 0.7445	1.211 ± 0.4189	0.092
Maximum body temperature			0.068
Low fever, n (%)	9(32)	12(63)	-
Moderate fever, n (%)	13(46)	5(26)	-
High fever, n (%)	6(21)	2(11)	-
Cough, n (%)	52(65)	29(97)	0.001
Expectoration, n (%)	45(56)	28(93)	< 0.001
Sore throat, n (%)	36(45)	12(40)	0.638
Dyspnea, n (%)	1(1)	0(0)	0.538
Diarrhea, n (%)	7(9)	3(10)	0.839
Vomiting, n (%)	8(10)	0(0)	0.072
Myalgia, n (%)	15(19)	8(27)	0.363
Weakness, n (%)	15(19)	16(53)	< 0.001
Taste/smell changes, n (%)	17(21)	9(30)	0.336

Abbreviations: SLE, systemic lupus erythematosus; COVID-19, coronavirus disease 2019; BMI, body mass index; DMARDs, traditional disease-modifying anti-rheumatic drugs

predicted that an epidemic driven by a superspreader would rapidly spread in cities but not in rural areas, mainly because the rural exodus limits the maximum number of secondary infections [19]. COVID-19 vaccination status was also collected, and no differences in vaccination status were found according to study group. A number of confounding factors may have confounded these results, such as vaccine type and regimen, vaccination schedule, completion of the full vaccination schedule, and the timing of the last vaccination. A number of previous studies have pointed out that these factors may affect the effectiveness of vaccines [20–22], but it is difficult for non-medical professionals to accurately describe the detail of vaccine they received, so the data in this part of the study were not collected completely, and future studies with specific medical records or medical insurance data are needed to supplement this exploration.

Based on the potential association between living environment and COVID-19, researchers conducted a statistical analysis of SLE patients using belimumab and their cohabitants. The statistical results suggested that the incidence of COVID-19 was similar between belimumab users and their cohabitants. Interestingly, SLE patients receiving belimumab treatment exhibited a reduction in COVID-19 symptoms compared to their cohabiting counterparts. As a humanized immunoglobulin IgG-1k monoclonal antibody, belimumab is capable of promoting apoptosis and inhibits the differentiation and survival of B cells by inhibiting the binding of soluble B-lymphocyte stimulator (BLyS) [23]. Several studies have demonstrated that higher levels of peripheral B cells and plasma cells are associated with disease exacerbation and poor outcomes in COVID-19 [24]. Additionally, single-cell transcriptome analysis of immune cells in bronchoalveolar lavage fluid from patients with SARS-CoV-2 infection has revealed that pulmonary macrophages from patients with severe COVID-19 express higher levels of BLyS, which promote B-cell activation and thus express more immunoglobulin genes, than those from patients with mild disease [25]. Thus, belimumab may partially alleviate COVID-19 symptoms by targeting BLyS to affect B cell responses. Notably, recent studies have suggested that IgD-CD27-, a specific double-negative B cell subset (DN B cells), may be involved in tissue inflammation and fibrosis in COVID-19 patients [26]. Belimumab acts on early developmental stage B cells to inhibit DN B differentiation to some extent has been confirmed by relevant studies [27], and the reduction of DN B cell differentiation has also been reported to play a role in the treatment of autoimmune diseases [27]. However, it should be noted that DN B cells are also divided into three subsets, among which SLE patients are mainly dominated by changes in DN2 subsets [28], while COVID-19 patients are mainly dominated by increases in DN3 [26], which may require further research to explore the correlation.

Several previous studies have suggested that belimumab has a long-term effect on the treatment of SLE [29, 30]. Findings have indicated that patients who last received belimumab less than a month prior or had a treatment gap of over three months before COVID-19 were more likely to have low and high fever, respectively. This observation may be attributed to the drug's half-life, which is reported to be approximately 18 days when administered subcutaneously [31]. This is similar to the results of our survey. The protective effect of belimumab on inhibiting fever in SLE patients infected with COVID-19 decreased in parallel to its serum half-life.

belimumab is known to affect the adaptive immune response [32] and cough and upper respiratory tract infections are common side effects of treatment with belimumab [29, 33]. Our observations showed that belimumab was the most frequently discontinued drug among SLE patients with COVID-19. Several studies do not provide clear recommendations on whether to continue or discontinue belimumab in patients with SLE and COVID-19 [34, 35]. In fact, the current guidelines suggest discontinuation of biologic agents after SARS-CoV-2 infection [36]. These factors may have influenced clinicians in advising SLE patients with COVID-19 to discontinue the use of belimumab. In our study, SLE did not worsen in patients who discontinued treatment.

Research strengths and innovations

This study has several advantages over previous reports: (1) this study provides an in-depth investigation of the impact of belimumab use in COVID-19; (2) the symptoms of COVID-19 were described and compared in detail, and the cohabitants of SLE patients were used as controls to exclude unwanted interferences; (3) the impact of drug withdrawal in SLE patients during COVID-19 was comparatively analysed; and (4) most of the SARS-CoV-2 positive patients in this study were densely infected in a similar period of time to avoid the bias of season and climate.

Limitations

However, this study also has some limitations: (1) it was a single-centre survey, which may have patient treatment and regional bias; (2) the information was mainly collected by telephone survey, which may have led to subjective neglect and exaggeration of symptoms by some subjects; (3) SLE patients receiving immunosuppressive therapy or biological agents may pay more attention to hygiene and distancing measures than the general population; (4) the number of subjects was small; and (5) the medication of SLE patients

is complicated, and multiple drugs are often used or stopped at the same time.

Conclusion

This study found that belimumab did not increase susceptibility to COVID-19; instead, it even partly reduced the COVID-19 symptoms of the users. This finding adds to the knowledge about the use of belimumab in patients with SLE during SARS-CoV-2 infection and helps inform the relevant authorities about the management and treatment of SLE. In the future, larger clinical cohorts or real-world studies are needed for verification, and more mechanistic explorations are desirable.

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Author contributions All authors contributed to the study conception and design. CYT and YL jointly proposed the study topic and jointly designed the study protocol with YHL. YLW and TW designed the questionnaire and screened the list of potential participants. DYH completed the relevant ethical review. JHW, WHZ, XJJ, and CQY followed up and verified the cohort patients by telephone according to the list and data. ZHL completed the data collation and induction. YLW, XPL, and LC performed the data analysis and interpretation of the results. YLW and YHL wrote the manuscript, and CYT, YL and MH revised the manuscript.

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Data availability All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This retrospective study received ethical approval from the Biomedical Ethics Committee of West China Hospital, Sichuan University. The approval number assigned to this study is 2023 (277). This study was a retrospective observational study, without any intervention in the process of patient care, and all data did not contain information that could identify the patient's identity and would not harm the patient's privacy, so informed consent was not applicable. The study did not involve animal studies, and no ethical approval was needed.

Ethics declarations This study was approved by the ethical committee of West China Hospital of Sichuan University (No. 277 in 2023) and complied with the Declaration of Helsinki.

Consent to participate Not applicable.

Consent to publish Not applicable.

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