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ORIGINAL ARTICLE

Effects of belimumab on the lipid profile in systemic lupus erythematosus patients: an observational study

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Abstract

This study is asked to investigate the effects of belimumab on the lipid profile in systemic lupus erythematosus (SLE) patients. Forty-one SLE patients who received at least 6 months of belimumab treatment were retrospectively analyzed. The control group consisted of 56 age- and sex-matched lupus patients not treated with belimumab. The changes in lipid profile after a 6-month treatment were compared between the two groups. Generalized estimating equation (GEE) analyses were performed to examine lipid levels longitudinally during the period and the effect of clinical response variables and medication on the lipid profile in the belimumab group. In the belimumab group, high-density lipoprotein (HDL) cholesterol levels increased significantly after the 6-month treatment ($P = 0.02$). After 1 month, HDL, apolipoprotein A-I (apoA-I) significantly increased by 13.8 and 11.4%, compared with baseline, respectively. After 3 months, HDL and apoA-I increased by 9.0 and 7.1%, respectively. After 6 months, HDL increased by 7.6% compared with baseline. Total cholesterol, triglycerides, low-density lipoprotein cholesterol, and apolipoprotein B did not change significantly over the course of treatment. GEE analyses indicated a significant association between HDL and disease activity indexes, such as IgG, anti-dsDNA, and complement C3. Subgroup analysis revealed significant changes in HDL only in patients who had achieved a ≥ 4-point reduction in SLEDAI-2 K after 6 months of belimumab treatment. Belimumab treatment may result in a long-term increase in HDL level in SLE patients by improving control of lupus activity. This might have beneficial effects on controlling cardiovascular risk in lupus patients.

Key Points
- *Treatment with belimumab resulted in a significant and sustained increase in the HDL levels in SLE patients.*
- *Significant changes in HDL were observed in lupus patients treated with belimumab who had a better clinical response.*

Keywords Belimumab · HDL · Lipid profile · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by B-cell hyperactivation and autoantibody production [1]. As is well known, the risk of cardiovascular disease (CVD) is increased in SLE. A recent systematic review indicates that the risk of CVD in SLE patients is about two- to three-fold compared with that in adults without SLE [2]. SLE patients also experience increased cardiovascular mortality, which is one of the leading causes of death [3]. Atherosclerosis (AS) is a multifactorial process, and as a traditional risk factor, lipid abnormalities may play a pivotal role in the development of AS. Lipid metabolism in SLE patients has been demonstrated to be disturbed, with high levels of triglycerides (TG), total cholesterol(TC), low-density lipoprotein (LDL) cholesterol, apolipoprotein B (apoB), and low levels of high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I (apoA-I) [4–7]. Inflammation, disease activity, and medicine may aggravate lipid abnormalities in SLE patients.

With the availability of biological drugs, the prognosis of rheumatic diseases has improved markedly, including a cardioprotective effect. Several biologics have been demonstrated to influence lipid and lipid metabolism, such as

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IL-6 receptor antagonists, TNF inhibitors, rituximab, and JAK inhibitors [8, 9]. B-lymphocyte stimulator (BLyS), also named B-cell activating factor (BAFF), is a cytokine that has a critical role in B-cell survival, maturation, and Ig production [10, 11]. BLyS overexpression may contribute to SLE pathogenesis [12]. Belimumab, a human monoclonal antibody targeting BLyS, has been approved for treating SLE in 2011 by FDA and in 2019 by sino-FDA. The role of BAFF in atherosclerosis is debated, with studies showing both protective and harmful effects. Genomic data suggested that the BAFF receptor pathway played a key role in coronary heart disease [13]. Deleting or blocking the BAFF receptor could reduce experimental atherosclerosis in mice [14, 15]. On the other hand, overexpression of BAFF had been shown to decrease atherosclerosis in hyperlipidemic mouse models [16]. Treatment with anti-BAFF antibodies had been found to increase atherosclerosis in mice [17]. The impact of BAFF on atherosclerosis in the lupus-prone backgroud of ApoE$^{-/-}$ mice depended on TC levels, BAFF neutralization improved atherosclerosis lesions in mice with low cholesterol levels but worsened the lesions in mice with high cholesterol levels [18].

BAFF is also known as an adipokine that links obesity and inflammation [19]. Increased serum BAFF was related to obesity-related metabolic alterations and endothelial dysfunction [20]. Studies on the impact of BAFF on lipids have produced conflicting results. BAFF overexpression in mice led to decreased VLDL levels without affecting HDL levels [16]. However, BAFF neutralization or blocking the BAFF receptor had no direct effect on lipids in hyperlipidemic mice [15, 17, 18].

In SLE patients, high levels of BAFF were associated with subclinical atherosclerosis [18]. Dyslipidemia is an initiating factor in the development of atherosclerosis, and the effects of anti-BAFF biologics on SLE patients' lipid profiles are unknown. A recent study from Greece found no significant changes in the lipid profile of 35 SLE patients treated with belimumab for 6 months [21]. Nevertheless, the absence of corroborative research necessitates further investigation. Due to the controversial role of BAFF in atherosclerosis and lipids in mouse models and limited availability of data in existing literature for clinical study, the present study seeks to explore alterations in lipid profiles among Chinese SLE patients undergoing belimumab treatment over an extended period.

Patients and methods

Paticipant selection

We conducted a retrospective longitudinal observation study. Data from SLE inpatients who initially received at least consecutive 6-month administration of belimumab between April 2020 and March 2023 were collected from the Zhongshan Hospital Xiamen University. SLE inpatients who did not receive belimumab or other biologic treatment during the same period were selected as the control group. Inclusion criteria were as follows: (1) patients with age more than 18 years; (2) patients fulfilled American College of Rheumatology or Systemic Lupus International Collaborating Clinics criteria [22]; and (3) availability of laboratory data regarding lipid profile at baseline and 6 months after the treatment. In the belimumab group, all patients were administered 10 mg/kg intravenous infusion of belimumab on days 0, 14, and 28 and every month for at least 6 months. This study was approved by the ethical committee of the Zhongshan Hospital Xiamen University (2023–105) and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from patients.

Data collection

Demographic, clinical features, laboratory data, and medication details were obtained at baseline. Medication details including the usage of prednisone, hydroxychloroquine (HCQ), and lipid-lowering drugs were collected at baseline, 1 month, 3 months, and 6 months in the belimumab group. The lipid profile included levels of TC, HDL, TG, LDL, apoB, and apoA-I. Lupus activity-related laboratory data included anti-dsDNA, lgG, complement C3, and C-reactive protein (CRP). Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2 K) data and modified Framingham risk score (mFRS) [23] were collected at baseline and 6 months.

Statistical analysis

The distribution of variables was tested for normality. Metric data are represented herein as mean ± standard deviation (SD) or median (p25, p75). Categorical data are represented herein in terms of frequency and composition. *T*-test or nonparametric Mann–Whitney test was used for the comparisons of the lipid levels at baseline. Paired two-sample *t*-test or the related sample Wilcoxon's signed-rank test was used for bivariate comparisons of changes in lipid levels, SLEDAI-2 K, and mFRS after 6 months. Spearman's rank correlation coefficient was calculated to investigate the association between the change in lipid levels and lupus activity. Owing to the longitudinal study design, we used GEE analyses to examine the differences in the lipid levels over time in belimumab group, as it can handle unequally spaced time intervals and missing data [24]. Additionally, GEE analyses were conducted to assess the impact of medication on the lipids. The lipid value was treated as a dependent variable in this analysis. Age, gender, and medication were adjusted

for this analysis as appropriate. A log transformation was performed for data with a skew distribution before GEE analyses, such as TG. GEE analyses were carried out by using the exchangeable correlation matrix. A p-value < 0.05 was considered statistically significant. All analyses were conducted with SPSS 21.0.

Results

Patient's characteristics at baseline

A total of 119 patients received belimumab treatment from April 2020 to March 2023 were reviewed, of whom, five were aged < 18 years, 47 did not receive continuous treatment for 6 months, and 23 stopped belimumab treatment within 6 months (2 [1.6%] because of inefficacy, 2 [1.6%] due to adverse events, and 19 [15.9%] were lost to follow-up, none for a CVD event), and lipid profile data were not available for three patients. Finally, 41 patients were enrolled in the belimumab group (age 35.3 ± 9.8 years, 97.6% females), with 56 patients in the control group (age 38.8 ± 10.6 years, 87.5% females). Characteristics at baseline are encapsulated in Table 1. All participants belonged to Han ethnicity. All patients did not receive any special dietary regimen during treatment. There were no significant differences in age, sex, SLE duration, and frequency of lupus nephritis between the two groups (all $P > 0.05$). No significant differences were observed in frequency of smoking, overweight or diabetes between the two groups (all $P > 0.05$). Baseline lupus activity-related data were not significantly different between the two groups, including SLEDAI-2 K, anti-dsDNA levels, IgG, and C3 (all $P > 0.05$). The frequency of concomitant treatment with HCQ, prednisone, and lipid-lowering drugs was reported with no significant statistical differences (all $P > 0.05$). In addition to prednisone and HCQ, other immunosuppressants used in the belimumab group included cyclophosphamide ($n = 1$, 2.4%), mycophenolate mofetil ($n = 3$, 7.2%), cyclosporin A ($n = 2$, 4.9%), tacrolimus ($n = 1$, 2.4%),leflunomide ($n = 1$, 2.4%), azathioprine ($n = 2$, 4.9%), and iguratimod ($n = 1$, 2.4%). There were no significant differences in the prednisone dose at baseline between the two groups (all $P > 0.05$). During the 6-month treatment, the mean daily prednisone dose did not show significant differences between the two groups (17.1 ± 11.1 vs. 15.4 ± 8.5, $P > 0.05$).

Changes in lipid levels

As shown in Table 2, the mean values of TC, HDL, LDL, apoA-I, and apoB were statistically not different between the groups at baseline (all $P > 0.05$). The median value of TG in the control group was significantly higher than in the belimumab group at baseline (1.34 (1.05–1.92) vs. 1.12 (0.88–1.72), $P = 0.04$) (Table 2).

Table 3 shows the changes in lipid levels between the two groups after 6 months of treatment. In the belimumab group, HDL levels increased significantly after the 6-month

Table 1 Characteristics of the patients at baseline

	Control ($n = 56$)	Belimumab ($n = 41$)	P value
Age, years	38.8 ± 10.6	35.3 ± 9.8	0.10
Female, n (%)	49 (87.5%)	40 (97.6%)	0.16
Current smokers, n (%)	2 (3.6%)	0 (0%)	0.51
BMI ≥ 25, n (%)	6 (10.7%)	2 (4.9%)	0.51
Diabetes mellitus, n (%)	0	1(2.4%)	0.42
Modified Framingham risk score (%)	3.9 (1.3–15.9)	2.4 (1–7.45)	0.17
SLE duration, years	2.0 (1.0–9.0)	6.0 (2.0–10.0)	0.09
Lupus nephritis, n (%)	21 (37.5%)	21 (51.2%)	0.18
SLEDAI-2 K	4.0 (2.0–11.0)	8.0 (4.0–12.0)	0.11
IgG, g/L	13.0 ± 6.8	14.5 ± 8.1	0.35
C3, g/L	0.74 ± 0.23	0.70 ± 0.28	0.50
Anti-dsDNA, IU/mL	100 (0–432)	57 (7.2–318.0)	0.82
Lipid-lowering drugs, n (%)	16 (28.6%)	7 (17.1%)	0.19
Statins, n (%)	15 (26.8%)	6 (14.6%)	0.15
Fibrates, n (%)	1 (1.8%)	1 (2.4%)	1.00
HCQ, n (%)	43 (76.8%)	37 (90.2%)	0.09
Prednisone use, n (%)	53 (94.6%)	39 (95.1%)	1.00
Prednisone dose, mg/day	15 (7.5–35)	20 (10–40)	0.27

Values are mean ± SD or median (p25–p75). *BMI* body mass index, *SLEDAI-2 K* Systemic Lupus Erythematosus Disease Activity Index 2000, *HCQ* hydroxychloroquine

Table 2 Lipid profile at baseline

	Control ($n=56$)	Belimumab ($n=41$)	P value
TC (mmol/L)	4.84 ± 1.31	4.79 ± 1.38	0.86
HDL (mmol/L)	1.32 ± 0.38	1.45 ± 0.42	0.11
TG (mmol/L)	1.34 (1.05–1.92)	1.12 (0.88–1.72)	0.04*
LDL (mmol/L)	3.14 ± 1.09	3.03 ± 0.97	0.61
ApoA-I (g/L)	1.41 ± 0.42	1.40 ± 0.36	0.96
ApoB (g/L)	0.91 ± 0.30	0.85 ± 0.27	0.26

Values are mean ± SD or median (p25–p75). *$P<0.05$. *TC* total cholesterol, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *TG* triglycerides, *apoA-I* apolipoprotein A1, *apoB* apolipoprotein B

treatment ($P=0.02$). After the 6-month treatment, the TG levels in the control group significantly decreased ($P=0.03$). The changes of TC, LDL, apoA-I, and apoB were not significantly different in both two groups after 6-month treatment (all $P>0.05$). There was a significant decline in SLEDAI-2 K in both the control group (baseline vs. 6 months: 4.0 vs. 3.0, $P<0.01$) and the belimumab group (baseline vs. 6 months: 8.0 vs. 4.0, $P<0.01$). The decreased SLEDAI-2 K showed no significant difference between the control group and the belimumab group (0 vs. 2, $P=0.11$). To further explore the association between TG and lupus activity in the control group, Spearman's rank correlation coefficients were calculated. We found statistically significant correlations between the reduction in TG levels and the reduction in SLEDAI-2 K after the 6-month treatment ($r=0.34$, $P=0.01$). To evaluate the impact of the change of HDL on CVD risk control, we chose modified Framingham risk score as a tool, and the belimumab group did not experience a significant change in mFRS (baseline vs. 6 months: 2.4 (1–7.45) vs. 1.6 (1–6.55) %, $P=0.21$).

Table 4 summarizes the changes in lipid levels over time in the belimumab group during 6-month treatment, as determined by performing GEE analysis adjusted for age and gender. After 4 weeks of treatment with belimumab, HDL increased by 13.8% ($P<0.001$). ApoA-I levels also increased by 11.4% compared with baseline ($P<0.001$). After 3 months, a significant increase in HDL and apoA-I was maintained. After 6 months, the level of HDL remained a 7.5% increase compared with baseline ($P=0.014$). After 6 months of treatment apoA-I exhibited, no significant difference compared with the baseline. TC, TG, LDL, and apoB did not change significantly throughout the treatment period.

Subgroup analysis in the belimumab group

Next, we attempted to further explore the effect of lupus disease activities on lipids in the belimumab group. To this end, we stratified the patients into two subgroups according to whether the patients had achieved a ≥ 4-point reduction in SLEDAI-2 K after 6 months of belimumab treatment. As shown in Table 5, significant changes in HDL were observed only in those patients who had a

Table 3 Lipoprotein level changes at 6 months

	Control ($n=56$)		Belimumab ($n=41$)	
	Mean differences (SD)	P	Mean differences (SD)	P
TC (mmol/L)	− 0.15 (1.27)	0.38	− 0.05 (0.91)	0.72
HDL (mmol/L)	0.08 (0.40)	0.15	0.11 (0.29)	0.02*
LDL (mmol/L)	− 0.15 (1.10)	0.33	− 0.05 (0.72)	0.64
ApoA-I (g/L)	0.04 (0.43)	0.49	0.08 (0.36)	0.19
ApoB (g/L)	− 0.08 (0.28)	0.05	− 0.02 (0.20)	0.53
	Mean differences; Z	P	Mean differences; Z	P
TG (mmol/L)[a]	− 0.28; − 2.13	0.03*	− 0.02; − 0.39	0.71

*$P<0.05$

[a]Wilcoxon signed-rank test conducted

Table 4 Changes in the lipid profile during treatment with belimumab

Variable	Baseline	1 month	3 months	6 months
TC (mmol/L)	4.79 ± 1.38	5.11 ± 1.34*	4.89 ± 1.07	4.74 ± 0.85
HDL (mmol/L)	1.45 ± 0.42	1.65 ± 0.38*	1.58 ± 0.33*	1.56 ± 0.32*
TG (mmol/L)	1.12 (0.88–1.72)	1.22 (0.88–1.56)	1.24 (0.87–1.54)	1.12 (0.74–1.42)
LDL (mmol/L)	3.03 ± 0.97	3.19 ± 0.94	3.07 ± 0.74	2.97 ± 0.61
apoA-I (g/L)	1.40 ± 0.36	1.56 ± 0.36*	1.50 ± 0.27*	1.49 ± 0.31
apoB (g/L)	0.85 ± 0.27	0.89 ± 0.27	0.86 ± 0.23	0.82 ± 0.20

Values are mean ± SD or median (p25–p75). *$P<0.05$ compared with baseline performed by GEE analyses

Table 5 Influence of clinical response on HDL levels in belimumab group

		Delta-SLEDAI-2 K ≥ 4 ($n = 19$)	Delta-SLEDAI-2 K < 4 ($n = 22$)
HDL (mmol/L)	Baseline	1.446 ± 0.386	1.457 ± 0.460
	1 month	+0.268***	+0.144**
	3 months	+0.205**	+0.065
	6 months	+0.167*	+0.064

Changes in lipid levels were calculated as changes from baseline. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. All values compared with the baseline performed by GEE analyses. Delta-SLEDAI-2 K, changes in SLEDAI-2 K after 6 months of belimumab treatment

better clinical response after 1, 3, and 6 months of belimumab treatment. ApoA-I increased in both groups after 1 month. However, no significant change was observed after 6 months compared with baseline (data not shown). ApoB levels significantly increased in deltaSLEDAI-2 K < 4 group after 1 month and 3 months but not in 6 months (data not shown). TC, TG, and LDL displayed no significant difference after treatment over time in both groups (data not shown herein).

Effects of disease activity indicators and medication on HDL and apoA-I in the belimumab group

As the change in HDL over time was significant and sustained during the belimumab treatment, we further explored the effects of lupus activity indicators and medication on HDL and apoA-I. After adjusting for age and gender, HDL levels were significantly associated with disease activity according to GEE analyses. HDL was positively correlated with C3 (regression coefficient = 0.247, $P = 0.033$), which implies that if C3 increases by 1 g/L, HDL will increase by 0.247 mmol/L. IgG and anti-dsDNA were significantly inversely associated with HDL (regression coefficient = − 0.032, $P < 0.001$, and regression coefficient = − 0.0002, $p = 0.004$, respectively). Likewise, a negative correlation was noted between apoA-I and IgG (regression coefficient = − 0.028, $P < 0.001$) and anti-dsDNA (regression coefficient = − 0.0002, $P = 0.015$). The inflammatory marker CRP and prednisone dose did not display a significant association with HDL and apoA-I. In the GEE analysis investigating the changes in the lipid profile at different time points, after adjustment for the usage of HCQ, antihyperlipidemic drugs, and the prednisone dose, the results corresponding to HDL levels did not change (data not shown herein).

Discussion

In this retrospective clinical study, we investigated the relationship between lipid profile and belimumab treatment in SLE patients. It appears that belimumab might have a beneficial effect on HDL levels of SLE patients.

Studies on the effect of biologics targeting B cells on patients' lipid profiles are limited, and their findings are inconsistent and contentious. Rituximab, a monoclonal antibody targeting B cell, is usually administered to refractory lupus patients. Two previous studies evaluated the change in lipid profiles in SLE patients who received rituximab treatment. One retrospective study reported that rituximab could increase HDL levels and decrease TG levels in SLE patients after 1 year of follow-up [25]. Another study demonstrated that TG levels were reduced after rituximab treatment for at least 6 months, whereas HDL levels remained unchanged [26]. Belimumab, a biologic targeting B cells, was confirmed to be effective in reducing SLE disease activity and facilitating glucocorticoid tapering [27, 28]. Recently, a study from Greece showed that the lipid profile did not significantly change in SLE patients treated with belimumab [21] In our study, adjusted GEE analysis indicated that HDL levels significantly increased after 1 month, 3 months, and 6 months of belimumab treatment. The disparities between the studies might be due to the heterogeneity between the groups of populations studied, in terms of age, smoking, and BMI. HDL cholesterol is known to have an atheroprotective effect and the ability to block LDL oxidation. Many pieces of evidence suggest that HDL levels are decreased and dysfunctional HDL is developed in SLE patients [29]. HDL-targeted therapies have been proposed as a potential therapeutic intervention in SLE patients with CVD [30, 31]. Although in this study, the change in HDL was small after 6 months treatment, it has been shown that every 0.026 mmol/L increment in HDL resulted in a 2–3% reduction in CVD risk [32]. It has been reported that patients with SLE have anti-HDL antibodies. High levels of anti-HDLwere associated with decreased levels of HDL in SLE patients [33]. There was also an association between anti-HDL and increased SLE disease activity and reduced HDL antioxidant and atheroprotective functions [34]. Similar results have also been reported in aging generalized lymphoproliferative disorder (GLD) mice, where reduced HDL was association with the development of autoimmunity, and the anti-apoA-I contributed to reducing HDL-C levels independent of hepatic HDL biogenesis [35]. Whether belimumab could increase HDL levels by decreasing the levels of antiantibodies targeting HDL still needs to be explored in the future. Since this is a retrospective study, we are unable to further investigate how HDL

functions change after belimumab treatment. However, a recent study indicated that belimumab may improve the atheroprotective properties of HDL in SLE patients, which suggested a favorable impact on CVD risk control [21].

Several studies have demonstrated that SLE patients have altered lipid profiles. Low levels of HDL, elevated very low-density lipoprotein (VLDL) cholesterol, and TGs have been defined as the "lupus pattern" [7]. In active SLE, an increment in TG and a decrement in HDL and LDL have been observed. One of the identified reasons is the lupus disease activity [7, 36, 37]. Recent evidence confirmed that SLE exerted a causal effect on lowering HDL and apoA-I [38, 39]. In our study in the control group with higher TG levels at baseline, a significant decrease in TG levels was observed after 6-month treatment without belimumab. The improvement in TG levels coincided with the decreased SLEDAI-2 K after 6 months treatment. It is possible that the change in TG levels was due to the improvement of SLE disease activity. Consistent with previous findings, in the belimumab group, we noted significant correlations between HDL and SLE disease activity indicators, such as IgG, anti-dsDNA, and C3. ApoA-I, as a main part of HDL, was significantly correlated with IgG and anti-dsDNA. In the subgroup analysis, as treatment time was prolonged, a significant improvement in HDL was only observed in patients who had better improvement in SLEDAI-2 K. It appears that the favorable effect of belimumab on HDL levels only applies to SLE patients who have a better response. Considering that belimumab does not directly affect lipid metabolism, it is likely that the beneficial effects on HDL levels are mediated by the improvement in disease activity.

Inflammation is believed to be involved in the development of dyslipidemia, and B cells play a role in production of inflammatory cytokines. However, in the belimumab group, we did not find a relationship between CRP and HDL or apoA-I. Whether belimumab can mediate the effects on lipids indirectly by reducing the production of inflammatory cytokines is still unknown.

We also explored the medication that may affect the level of HDL, including antihyperlipidemic drugs, HCQ, and prednisone. HCQ usage has been reported to increase HDL levels in lupus patients [40]. However, adjustment of antihyperlipidemic drugs and HCQ application did not change the significant results concerning the changes in HDL in the GEE analyses. The corticosteroid therapy increased TC, LDL, and TG in lupus patients [37]. In this study, no significant association was observed between prednisone and HDL level. The mean daily prednisone dose did not show significant differences between the two groups during the 6-month treatment. Adjustment of the daily dosages of prednisone did not change the result corresponding to HDL at different timepoints (data not shown herein). Thus, a reduction in steroid dose is unlikely to explain the improvement in HDL levels of the belimumab group.

This study has a few limitations. First, due to the retrospective nature of this study, there may have been selection bias at the baseline. Second, as the number of subjects was small, limited adjustment was made for covariables due to its small sample size. Third, possible bias of this study is the relatively short observation time. Fourth, because a large proportion of the data of 24-h urine protein was missing, we did not analyze the effect of urine protein on lipid profile.

In summary, belimumab treatment may have resulted in a long-term increase on the level of HDL in SLE patients by improving control of lupus activity. Prospective studies are required to establish whether belimumab treatment results in a lower cardiovascular risk.

Author contributions DL and RD designed this study. SH and DL collected the data and performed the statistical analysis. DL drafted the manuscript. The final manuscript was read and approved by all authors.

Data availability The datasets used or analyzed in this study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate This study was approved by the ethical committee of the Zhongshan Hospital Xiamen University (2023–105) and was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

Disclosures None.

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