Sirolimus versus tacrolimus for systemic lupus erythematosus treatment: results from a real-world CSTAR cohort study

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ABSTRACT

Objective The effectiveness and safety of sirolimus for SLE treatment have been shown in some uncontrolled studies. However, a comparison of sirolimus with other classic immunosuppressants has not been reported. We conducted the study to compare the effectiveness and safety of sirolimus versus tacrolimus for SLE treatment.

Methods A real-world cohort study was conducted. Patients with clinically active SLE who were prescribed sirolimus or tacrolimus were enrolled. Propensity score matching was used to ensure equivalent disease conditions and background medications. SLE disease activity indices, serological parameters, steroid doses, modification of other immunosuppressants, renal effectiveness and adverse events were compared between the two groups at 3-month, 6-month, 9-month and 12-month follow-up visits.

Results Data from 52 patients in each of the sirolimus and tacrolimus groups were analysed. Indices regarding the effectiveness of sirolimus, including Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) scores, physician's global assessment (PhGA) scores, and proportion of patients with SLEDAI-2K reduction of ≥4 and PhGA increase of <0.3, were equivalent to those of tacrolimus at all follow-up timepoints (all p≥0.05). Greater improvements in complement levels were observed in the sirolimus group at 3 and 6 months. Higher percentages of patients with prednisone doses ≤7.5 mg/day were observed in the sirolimus group at all timepoints. Seventeen adverse events in the sirolimus group were recorded. None was severe or led to drug discontinuation.

Conclusions Overall, sirolimus was as effective as tacrolimus in the treatment of SLE. Sirolimus had better effects on serological improvement and glucocorticoid tapering. Sirolimus was well tolerated in patients with SLE.

INTRODUCTION

SLE is a complicated autoimmune disease that can result in morbidity, poor quality of life and death.[1 2] Organ damage and mortality can be caused by both the active disease itself and the adverse effects of medications. Remission and lupus low disease activity state (LLDAS) have been recently defined[3 4]

Key messages

What is already known about this subject?
► The clinical effectiveness of sirolimus (rapamycin) in SLE treatment has been observed in several uncontrolled studies.

What does this study add?
► The present study enabled a comparison of sirolimus and tacrolimus, which is a widely used immunosuppressant for SLE.
► Our results indicated that sirolimus was as effective as tacrolimus for SLE and has better effects on serological improvement and steroid tapering.
► This study used propensity score matching to match patients who were treated with sirolimus and tacrolimus in a large real-world cohort, enabling a credible comparison of the effectiveness of the two drugs.

How might this impact on clinical practice or future developments?
► The results of the present study indicated that sirolimus was effective and safe as a potential new therapeutic choice for SLE.

and have become widely accepted treatment targets proven to protect patients from damage accrual.[5–7] SLE medications include glucocorticoids, antimalarials, conventional immunosuppressants and biologics; many of these have been recommended and proven effective for the treatment of SLE.[8 9] However, considering the great heterogeneity of the disease and the significant adverse effects of current medications, more effective and safer medications are necessary.

Sirolimus—also known as rapamycin—is an inhibitor of the mechanistic (or mammalian) target of rapamycin (mTOR). Studies show that it has both mechanical and clinical therapeutic effects on SLE.[10–16] However, as a newly used medicine for SLE, more evidence and comparisons with other immunosuppressants are necessary to prove its efficacy and safety.
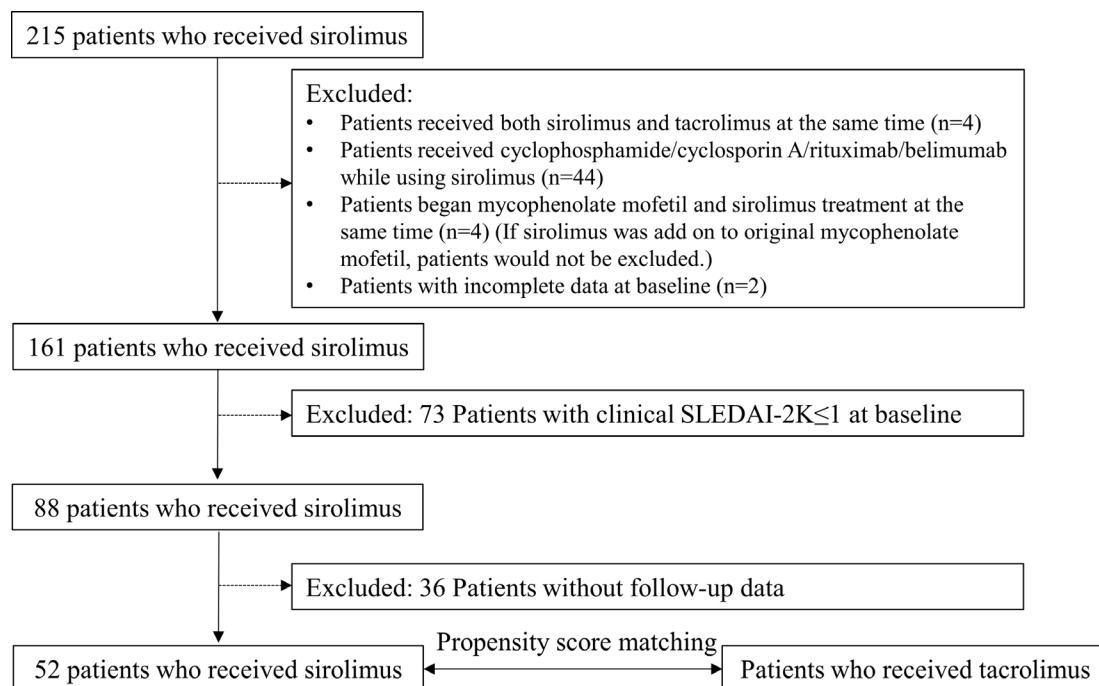
Figure 1 Screening flow chart. SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Tacrolimus, which is a calcineurin inhibitor, has a similar structure to sirolimus but a different therapeutic target. Its efficacy for SLE treatment has been widely acknowledged.[17–19] Based on the Chinese SLE Treatment and Research (CSTAR) group, which is the largest registry of SLE in China, we conducted a retrospective real-world cohort study to compare the effectiveness and safety of sirolimus versus tacrolimus.

METHODS
Patients
Until October 2020, 317 rheumatology centres in 31 provinces across China had participated in the CSTAR registry. Patients with SLE were recruited based on fulfilment of the 1997 American College of Rheumatology revised SLE classification criteria[20] or the 2012 Systemic Lupus International Collaborating Clinics SLE classification criteria.[21] As the leading centre of the CSTAR registry, Peking Union Medical College Hospital took on substantial responsibilities for training, communication and funding of the registry. Informed consent was provided by all patients. Neither patients nor the public were involved in the design, conduct, reporting or dissemination plans of our research. Until October 2020, 215 patients in the CSTAR cohort had been prescribed sirolimus. These patients were screened according to the inclusion and exclusion criteria (figure 1). Clinically active SLE was defined as a clinical Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[22] score of ≥2 (not including items relating to complement and anti-double-stranded DNA (anti-dsDNA) antibody levels). Finally, 52 patients who received sirolimus were enrolled in this study. Patients who received tacrolimus were screened following the same procedure and then matched to patients in the sirolimus group.

Data collection
All CSTAR centres used the same protocol-directed methods to both perform uniform evaluations and record patients' data. Investigators received training on diagnosis confirmation, disease activity evaluation, data input and data quality control. In this longitudinal study, data regarding demographic information, clinical features, laboratory examinations and SLE medications were collected at baseline, 3 months, 6 months, 9 months and 12 months. Clinical features included organ involvement, SLEDAI-2K and physician's global assessment (PhGA). Clinical response was defined as ≥4-point reduction in SLEDAI-2K with <0.3-point increase in PhGA. Clinical remission on therapy was defined as SLEDAI-2K score of 0 and PhGA of <0.5, with an allowed glucocorticoid dose of ≤5 mg/day (prednisone or equivalent). LLDAS was defined as the following: (1) SLEDAI-2K score of ≤4 with no scores for the renal, central nervous system, serositis, vasculitis or constitutional components; (2) no increase in any component since the previous visit; (3) PhGA of ≤1; and (4) glucocorticoid dose of ≤7.5 mg/day (prednisone or equivalent). Hydroxychloroquine and maintenance immunosuppressants were allowed for both definitions. For evaluation of renal effectiveness, complete renal remission was defined according to the Aspreva Lupus Management Study[23] as 24-hour urine protein (24hUP) <0.5 g, normal urinary sediment and serum creatine within 15% of the baseline value. Partial renal remission was defined as a 50% reduction in 24hUP, a 24hUP of <3.5 g and serum creatine within 25% of the baseline value.

Statistical analysis

All statistical analyses were performed using SAS V.9.4. Propensity score matching was used to match patients in the two groups. Sex, age at baseline, age of onset, age of diagnosis and SLE disease duration were defined as independent variables and use of sirolimus was defined as the dependent variable. Propensity score was calculated with logistic regression. The case to control ratio was set to 1:1. The optimal matching method was used to minimise the Mahalanobis distance of the logit of the propensity score. Data regarding effectiveness and safety of sirolimus versus tacrolimus were compared between the two groups. Quantitative variables were described using mean or median and were analysed with Student's t-test or non-parametric test according to their distributions. Categorical variables were described using counts and percentages and were analysed with χ^2 test or Fisher's exact test, as appropriate. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

After propensity score matching, 52 patients who received tacrolimus were matched to 52 patients who received sirolimus. As shown in table 1, there was no significant difference in baseline demographic, clinical or therapeutic features after matching.

Effectiveness of sirolimus versus tacrolimus

Data regarding the effectiveness of sirolimus versus tacrolimus at 6 months are shown in table 2. Data at 3, 9

Table 1 Pre-PSM and post-PSM characteristics of the tacrolimus and sirolimus groups at baseline

	Pre-PSM			Post-PSM		
	Tacrolimus (n=356)	Sirolimus (n=52)	P value	Tacrolimus (n=52)	Sirolimus (n=52)	P value
Female, n (%)	327 (89.59)	43 (82.69)	0.141	43 (82.69)	43 (82.69)	1.000
Age	32.13±10.28	38.37±11.47	0.000	37.62±11.21	38.37±11.47	0.737
Disease duration (years)	5.00 (2.00, 9.00)	6.00 (2.00, 9.00)	0.299	6.00 (1.50, 9.50)	6.00 (2.00, 9.00)	0.737
ANA positive, n (%)	350 (95.89)	51 (98.08)	0.705	50 (96.15)	51 (98.08)	1.000
ACL positive, n (%)	38/239 (15.9)	5/42 (11.9)	0.645	5/35 (14.3)	5/42 (11.9)	1.000
Anti-β2GPI positive, n (%)	33/228 (14.5)	6/41 (14.6)	1.000	4/30 (13.3)	6/41 (14.6)	1.000
LA positive, n (%)	39/185 (21.1)	3/37 (8.1)	0.070	5/25 (20.0)	3/37 (8.1)	0.250
C3	0.76 (0.56, 1.00)	0.74 (0.55, 0.96)	0.458	0.77 (0.61, 0.94)	0.74 (0.55, 0.96)	0.385
C4	0.14 (0.09, 0.22)	0.13 (0.09, 0.20)	0.592	0.15 (0.11, 0.25)	0.13 (0.09, 0.20)	0.171
Elevated anti-dsDNA, n (%)	154 (42.19)	30 (57.69)	0.035	24 (46.15)	30 (57.69)	0.239
SLEDAI-2K	7.74±5.08	8.27±3.08	0.020	7.88±5.67	8.27±3.08	0.079
PhGA	1.21±0.61	1.10±0.56	0.211	1.21±0.63	1.10±0.56	0.345
Mucocutaneous involvement, n (%)	236 (64.66)	32 (61.54)	0.660	34 (65.38)	32 (61.54)	0.684
Musculoskeletal involvement, n (%)	176 (48.22)	27 (51.92)	0.617	23 (44.23)	27 (51.92)	0.432
Haematological involvement, n (%)	147 (40.27)	30 (57.69)	0.017	22 (42.31)	30 (57.69)	0.117
Serositis, n (%)	243 (66.58)	30 (57.69)	0.208	36 (69.23)	30 (57.69)	0.222
Lupus nephritis, n (%)	237 (64.93)	26 (50)	0.037	34 (65.38)	26 (50)	0.112
Haematuria, n (%)	152 (41.6)	20 (38.5)	0.764	24 (46.2)	20 (38.5)	0.552
NPSLE, n (%)	10 (2.74)	2 (3.85)	0.652	1 (1.92)	2 (3.85)	1.000
Gastrointestinal involvement, n (%)	5 (1.37)	1 (1.92)	0.553	1 (1.92)	1 (1.92)	1.000
Eye involvement, n (%)	2 (0.55)	0 (0)	1.000	0 (0)	0 (0)	N/A
Cardiovascular involvement, n (%)	16 (4.38)	2 (3.85)	1.000	3 (5.77)	2 (3.85)	1.000
Pulmonary involvement, n (%)	3 (0.82)	2 (3.85)	0.119	0 (0)	2 (3.85)	0.495
GC usage, n (%)	336 (92.05)	44 (84.62)	0.078	44 (84.62)	44 (84.62)	1.000
GC dose (mg/day)	13 (8, 30)	12 (8, 22)	0.249	15 (10, 30)	12 (8, 22)	0.109
HCQ, n (%)	281 (76.99)	39 (75)	0.751	35 (67.31)	39 (75)	0.387
MMF, n (%)	103 (28.22)	13 (25)	0.628	11 (21.15)	13 (25)	0.642
Other IS, n (%)	35 (9.59)	11 (21.15)	0.013	4 (7.69)	11 (21.15)	0.051
Tacrolimus dose (mg/day)	2±1	N/A	N/A	2±1	N/A	N/A
Sirolimus dose (mg/day)	N/A	1.03±0.31	N/A	N/A	1.03±0.31	N/A

ACL, anticardiolipin antibody; anti-dsDNA, anti-double-stranded DNA; GC, glucocorticoid; HCQ, hydroxychloroquine; IS, immunosuppressant; LA, lupus anticoagulant; MMF, mycophenolate mofetil; N/A, not applicable; NPSLE, neuropsychiatric SLE; PhGA, physician's global assessment; PSM, propensity score matching; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; β2GPI, β2-glycoprotein I.

Table 2 Effectiveness of tacrolimus versus sirolimus at 6 months

	Tacrolimus	Sirolimus	P value
Change in SLEDAI-2K	−4.00 (−8.00, −4.00)	−6.00 (−8.00, −3.00)	0.489
SLEDAI-2K reduction ≥4 and PhGA increase <0.3, n (%)	19/25 (76)	18/24 (75)	1.000
Change in PhGA	−0.30 (−0.80, 0.20)	−0.50 (−0.90, 0.10)	0.480
PhGA reduction ≥0.3, n (%)	12/25 (48)	13/23 (56.52)	0.578
Clinical remission on therapy, n (%)	0 (0)	0 (0)	N/A
Remission or LLDAS, n (%)	2/21 (9.52)	5/21 (23.81)	0.410
Change in C3 (g/L)	0.10 (−0.07, 0.36)	0.28 (0.06, 0.48)	**0.042**
Change in C3 (%)	5.43 (−6.40, 20.57)	31.11 (6.26, 67.98)	**0.022**
Change in C4 (g/L)	0.01 (−0.03, 0.03)	0.07 (0.01, 0.11)	**0.005**
Change in C4 (%)	3.88 (−15.30, 17.86)	57.89 (5.80, 100.00)	**0.002**
Recovered hypocomplementaemia, n (%)	18/28 (64.29)	28/36 (77.78)	0.272
Normalised anti-dsDNA, n (%)	10/22 (45.45)	8/28 (28.57)	0.249
Change in GC dose (mg/day)	−2.50 (−12.00, 0.00)	−4.00 (−12.50, 0.00)	0.522
Change in GC dose (%)	−20.00 (−50.00, 0)	−34.00 (−63.64, 0)	0.260
No GC use, n (%)	0 (0)	0 (0)	N/A
GC dose ≤7.5 mg/day prednisone, n (%)	6/21 (28.57)	15/22 (68.18)	**0.015**
Renal effectiveness			0.627
Complete remission, n (%)	2/5 (40)	4/8 (50)	
Partial remission, n (%)	2/5 (40)	2/8 (25)	
No remission, n (%)	1/5 (20)	2/8 (25)	
Change in 24hUP	−4.05 (−5.59, 3.00)	−1.23 (−1.53, −0.22)	**0.023**
Haematuria, n (%)	7/25 (28.0)	8/24 (33.3)	0.762

P values in bold are statistically significant.

anti-dsDNA, anti-double-stranded DNA; GC, glucocorticoid; 24hUP, 24-hour urine protein; LLDAS, lupus low disease activity state; N/A, not applicable; PhGA, physician's global assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

and 12 months are shown in online supplemental tables 1-3. Both drugs showed good effectiveness in treating SLE. In most indices, including change in SLEDAI-2K, change in PhGA, percentages of patients with PhGA reduction ≥0.3 and percentages of remission, the two drugs showed identical effectiveness (p≥0.05). The proportions of patients with SLEDAI-2K reduction ≥4 and PhGA increase <0.3 and the proportions of patients who achieved remission or LLDAS were also equivalent in the two groups (figure 2).

More improvements in C3 and C4 levels were observed in the sirolimus group at 3 and 6 months (25% vs 8% elevation in C3 and 35% vs 11% elevation in C4 at 3 months, p=0.034 and p=0.017; 31% vs 5% elevation in C3 and 58% vs 4% elevation in C4 at 6 months, p=0.022 and p=0.002). The same tendencies were seen at 9 and 12 months; however, they were not significant. Significantly higher percentages of patients with prednisone doses ≤7.5 mg/day were observed in the sirolimus group at all four follow-up timepoints (49% vs 18% with p=0.010, 68% vs 29% with p=0.015, 79% vs 33% with p=0.025, and 85% vs 35% with p=0.009, at 3, 6, 9 and 12 months, respectively).

As for renal effectiveness, the ratios of complete or partial renal remission were identical at all follow-up visits, while tacrolimus showed better effectiveness in reducing urine protein at 6 months. During the follow-up period, the percentages of patients with haematuria were reduced in both groups at 6 months and no difference was observed between the two groups.

None of the 104 patients switched to the other group or to other immunosuppressants during their follow-up. Two patients in the tacrolimus group added sirolimus to their treatment at 3 and 12 months, respectively. Two patients in the sirolimus group added tacrolimus to their treatment at 12 months. Ciclosporin A was added to one patient's treatment in the sirolimus group at 9 months. Cyclophosphamide was added to two patients' treatment in the tacrolimus group and to one patient's treatment in the sirolimus group. No patient received belimumab or rituximab during follow-up.

Safety of tacrolimus versus sirolimus

In the sirolimus group, 17 adverse events in 15 patients were observed, including 2 cases of mild infections, 1 of mild haemocytopaenia, 1 of mild renal insufficiency, 3 of gastrointestinal discomforts, 3 of skin rashes, 4 of menstruation changes, 1 of mouth ulcer, 1 of facial oedema and 1 of alopecia. In the tacrolimus group, there
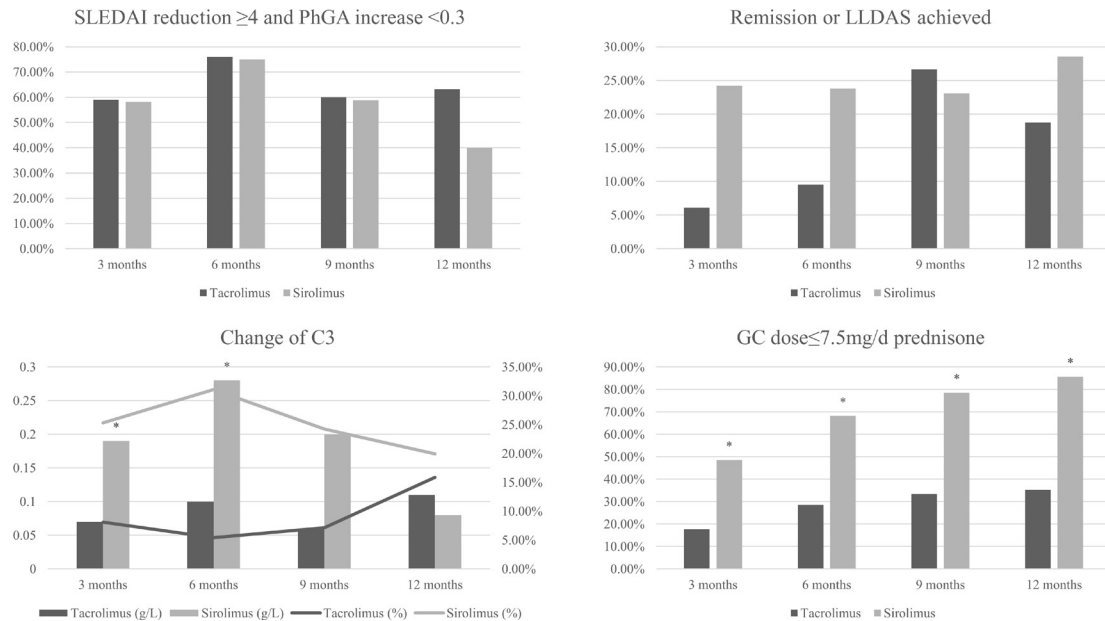
Figure 2 Indices regarding the effectiveness of sirolimus versus tacrolimus. GC, glucocorticoid; LLDAS, lupus low disease activity state; PhGA, physician's global assessment; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; *significantly different with tacrolimus group.

were three adverse events in three patients, including one case of mild infection, one of mild haemocytopaenia and one of loss of eyebrows and eyelashes. No severe adverse events were observed and no event led to discontinuation of sirolimus or tacrolimus.

DISCUSSION

This study is a real-world cohort study that compared the effectiveness and safety of sirolimus with tacrolimus for clinically active SLE. Sirolimus showed similar overall effectiveness to tacrolimus but better effectiveness in serological improvement and steroid tapering. More adverse events were observed in the sirolimus group than in the tacrolimus group, but none was severe or resulted in discontinuation of sirolimus.

Sirolimus, which is an mTOR inhibitor, has been successfully used for graft-versus-host disease prevention and for treatment of several autoimmune disorders. Its effectiveness and safety in SLE treatment have been reported in uncontrolled studies.[13–16] However, a comparison of sirolimus with other classic immunosuppressants has not been reported. In our study, tacrolimus was chosen as the positive control due to its structural similarities with sirolimus and its proven effectiveness as a medication recommended for SLE treatment according to several guidelines.[8 24 25] We believe that comparison with tacrolimus could help to properly determine the effectiveness of sirolimus. Propensity score matching was used to ensure that patients had similar baseline conditions.

SLEDAI and PhGA are well-accepted indices for evaluating SLE disease activity. In this study, there were remarkable and equivalent reductions in SLEDAI and

PhGA scores in both groups at all follow-up timepoints. The Systemic Lupus Erythematosus Responder Index 4 (SRI4) is a novel index for evaluating treatment response in patients with SLE.[26] SRI4 response is defined as the following: ≥4-point reduction in the Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI, <0.3-point increase in PhGA, no new British Isles Lupus Assessment Group (BILAG) score,[27] and no BILAG organ domain score or two new BILAG B organ domain scores. Lai et al[13] reported a 66% response rate at 12 months in patients receiving sirolimus. Referring to SRI4, we analysed the proportions of patients who achieved ≥4-point reduction in SLEDAI-2K with <0.3-point increase in PhGA (although the BILAG Disease Activity Index was not used in this study). Similar good responses were observed in both groups.

While clinical remission is a strict treatment goal in SLE, no patient in either group achieved remission at 3 or 6 months, and only a few patients achieved remission at 9 and 12 months. Thus, as an alternative treatment target, LLDAS was more achievable. The proportions of patients who achieved remission or LLDAS were similar in the two groups. Higher percentages in the sirolimus group were seen at 3, 6 and 12 months, but were not significant. Hence, larger sample size and longer follow-up period may be necessary to see larger percentages of LLDAS or clinical remission.

Anti-dsDNA antibody and complements are important activity-related markers. The percentages of patients whose anti-dsDNA turned negative during follow-up were not different between the two groups. Nevertheless, elevations in C3 and C4 (at 3 and 6 months) in the sirolimus group were significantly higher than those in

the tacrolimus group, which indicated better effectiveness for serological improvement in the early stage of treatment.

In addition to disease activity, steroid dose is an important index for measuring the effectiveness of an immunosuppressant. At all timepoints, the percentages of patients whose prednisone doses (or equivalent) were ≤7.5 mg/day were significantly higher in the sirolimus group. This result suggests that sirolimus may be more effective in steroid tapering.

Yap et al[14] reported the long-term effectiveness of sirolimus for treatment of lupus nephritis. In a long-term follow-up study, significant improvements in proteinuria and haematuria were observed in patients with SLE who received sirolimus.[28] Tacrolimus is an effective medication for treatment of lupus nephritis, especially for reduction of urine protein.[17–19 25] In our study, the renal effectiveness of sirolimus was compared with that of tacrolimus. Our results showed their similar effectiveness in achieving complete and partial renal remission and in reducing haematuria. Tacrolimus was found to be significantly more effective in reducing 24hUP at 6 months, and the same tendency was observed at other timepoints. It is probable that sirolimus is not as effective in reducing urine protein as calcineurin inhibitors. The number of patients with renal involvement was relatively small. Hence, a larger sample size would be necessary to fully investigate the effects on patients with renal involvement.

A recent systematic review and meta-analysis analysed the data of 145 patients from 9 studies.[29] In 111 clinically active patients, the pooled decrease in SLEDAI and prednisone dosages was 4.85 and 13.17 mg/day, respectively. The results indicated the good effectiveness of sirolimus in disease activity control and steroid tapering. In our study, similar results were observed, and comparison with tacrolimus provided more credible and quantifiable results.

Sirolimus was well tolerated in this study. Although more adverse events were reported in the sirolimus group, all were mild or moderate and did not result in drug discontinuation. The safety of sirolimus as an immunosuppressant has been proven in other immunity-related diseases. More data are required in the future to assess its safety in SLE treatment.

The limitations of this study include the following. First, the sample size was not large enough. Some differences, especially the advantages of sirolimus over tacrolimus, may be obscured due to sample size. Nevertheless, since sirolimus is a novel SLE medication, we believe that our data have provided valuable information for specialists. Hence, further study with a larger sample size will be conducted. Second, as previously mentioned, the BILAG Disease Activity Index was not included; thus, accurate SRI4 could not be recorded. We used ≥4-point reduction in SLEDAI-2K with <0.3-point increase in PhGA to measure treatment response and there might be slight deviations. Third, serum sirolimus concentration was not recorded, and the relationships between serum concentration and effectiveness or adverse effects were not analysed. Fourth, cholesterol and triglyceride levels were not recorded in this study; thus, we could not assess the incidence of dyslipidaemia, which is a commonly reported adverse effect of sirolimus. Fifth, antiphospholipid antibodies were not tested during the follow-up period. Previous studies with sirolimus showed improvement of antiphospholipid antibody levels,[13] and sirolimus was reported to be effective in antiphospholipid nephropathy in patients with renal transplantation.[30] It is worthy to comprehensively collect data regarding antiphospholipid antibodies in further follow-up to show the effect of sirolimus on antiphospholipid antibodies. Sixth, in this real-world study, there might have been some bias in the recording of adverse events. Since sirolimus is a relatively new drug for SLE, rheumatologists might not have been very familiar with its adverse effects. Distinguishing adverse effects from SLE disease activity was a challenge. Physicians might have recorded all abnormal situations as adverse events to avoid missing any adverse effects of sirolimus. Therefore, there might have been an overestimation of the adverse effects of sirolimus. Rigorous judgement and assessment of adverse events should be conducted in future randomised controlled trials.

In conclusion, we conducted the first study comparing the effectiveness and safety of sirolimus in the treatment of SLE with that of a classic immunosuppressant. Sirolimus and tacrolimus showed equivalent effectiveness in disease activity control, and sirolimus showed better effectiveness in terms of serological improvement and glucocorticoid tapering. Sirolimus was well tolerated in patients with SLE. We believe that sirolimus is effective and safe for SLE treatment.

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