Success and Associated Factors of Steroid Withdrawal in Patients with Systemic Lupus Erythematosus at Ratchaburi Hospital, Thailand

ความสำเร็จการหยุดยาสเตียรอยด์และปัจจัยที่สัมพันธ์กับความสำเร็จการหยุดยาของผู้ป่วยลูปัสในโรงพยาบาลราชบุรี

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Abstract

Objective: The study aimed to examine the success and associated factors of steroid withdrawal in patients with systemic lupus erythematosus (SLE) at Ratchaburi Hospital, Thailand.

Methods: A retrospective study based on medical records included consecutive patients with SLE who attended the outpatient unit in Ratchaburi Hospital. The success rate of steroid withdrawal without resuming in 1 year was studied and the associated factors were determined. Logistic regression was used to analyze the data.

Results: At Ratchaburi Hospital, 569 patients with SLE were treated with glucocorticoids and followed up for more than 1 year between September 2016 and August 2020. Of these, 200 patients (35.1%) who discontinued prednisolone were included in our study. Of the 200 patients, 87.5% were female. The mean (SD) age was 42.1 (14.0) years. The median SLE disease duration was 28.5 (ranging from 1 to 278) months. The success rate of steroid withdrawal was 89.5%. The findings from the univariate analysis revealed that some factors were associated with success, such as the use of antimalarial drugs at the time of steroid withdrawal, higher BMI, and slow reduction of steroids by decreasing prednisolone below 5 mg/day for more than 12 weeks before stopping with OR 29.67 (95% CI 2.93–300.23), 1.13 (95% CI 1.01–1.23), and 25.44 (95% CI 8.41–76.93) respectively.

Conclusion: The present study reported a high rate of steroid withdrawal success without the need to resume steroid use in a year. The use of antimalarial drugs, a higher BMI, and gradual

reduction of prednisolone below 5 mg/day for more than 12 weeks before stopping were found to be associated with success. The study showed the feasibility of steroid withdrawal, and its implications could be useful in planning the SLE management.

Keywords: success steroid withdrawal, systemic lupus erythematosus, antimalarial drugs
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บทคัดย่อ

วัตถุประสงค์: ศึกษาความสำเร็จและปัจจัยที่สัมพันธ์กับความสำเร็จการหยุดยาสเตียรอยด์ของผู้ป่วยลูปัสในโรงพยาบาลราชบุรี

วิธีการศึกษา: การศึกษาครั้งนี้เป็นการศึกษาย้อนหลังโดยใช้ข้อมูลจากการทบทวนเวชระเบียนผู้ป่วยโรคลูปัสที่เข้ารับการรักษาที่แผนกโรงพยาบาลราชบุรี โดยศึกษาอัตราความสำเร็จของการหยุดสเตียรอยด์ และปัจจัยที่เกี่ยวข้องกับความสำเร็จการหยุดยา ใช้วิธีวิเคราะห์ข้อมูลใช้การถดถอยโลจิสติก

ผลการศึกษา: ระหว่างเดือนกันยายน พ.ศ. 2559 ถึงเดือนสิงหาคม พ.ศ. 2563 พบผู้ป่วยลูปัสได้รับการรักษาด้วยสเตียรอยด์และการรักษามากกว่า 1 ปี 569 คน โดยนำ 200 คน หรือคิดเป็น ร้อยละ 35.1 ที่หยุดสเตียรอยด์เข้าในการศึกษานี้ เป็นผู้ป่วยเพศหญิงร้อยละ 87.5 อายุเฉลี่ย 42.1 ปี เป็นโรคลูปัสนาน (ค่ามัธยฐาน) 28.5 เดือน สามารถหยุดยาสเตียรอย์ได้ร้อยละ 89.5 โดยเมื่อวิเคราะห์ความสัมพันธ์โดยใช้การถดถอยโลจิสติกแบบปัจจัยเดียวพบว่า ปัจจัยที่มีนัยสำคัญทางสถิติ ได้แก่ การใช้ยาต้านมาลาเรียร่วมด้วย ดัชนีมวลกายสูง และการลดสเตียรอยด์อย่างช้าๆ โดยลดยาเพรดนิโซโลนต่ำกว่า 5 มิลลิกรัมต่อวัน มากกว่า 12 สัปดาห์ก่อนหยุดยา โดยมี OR 29.67 (95% CI 2.93–300.23), 1.13 (95% CI 1.01–1.23), และ 25.44 (95% CI 8.41–76.93) ตามลำดับ

สรุป: การศึกษานี้รายงานอัตราความสำเร็จของการหยุดยาสเตียรอยด์ได้สูงในผู้ป่วยลูปัส และพบปัจจัยที่เกี่ยวข้องกับความสำเร็จการหยุดยา กล่าวคือ การใช้ยาต้านมาลาเรีย ดัชนีมวลกายที่มากขึ้นและการลดการใช้ยาสเตียรอยด์ต่ำกว่า 5 มิลลิกรัมต่อวัน มากกว่า 12 สัปดาห์ การศึกษานี้แสดงถึงความเป็นไปได้ของการหยุดสเตียรอยด์และอาจนำไปใช้เป็นข้อมูลในการวางแผนการรักษาผู้ป่วยโรคลูปัสได้

คำสำคัญ: โรคลูปัส ยาสเตียรอยด์ ความสำเร็จการหยุดยา ยาต้านมาลาเรีย
วารสารแพทย์เขต 4-5 2567 ; 43(1) : 1–11.

Introduction

Systemic lupus erythematosus (SLE) is a complex, heterogeneous autoimmune disease that involves inflammatory processes in multiple organs, resulting in a broad range of clinical phenotypes from mild to severe. It is a remitting and relapsing disease with substantial patient-to-patient variation in clinical and serological manifestations and treatment response[1]. SLE is more common in females

than in males, with a ratio of 2–15 times, and the age of onset is 20–40 years old. The prevalence of SLE in Asia is approximately 10–90 per 100,000 people[2]. The hallmark of the disease is the formation of autoantibodies resulting in immune complex deposition, complement activation, and end-organ failure[1]. Some of the mechanisms behind this cascade include loss of immune tolerance, increased antigenic load, excess T-cell help, defective B-cell suppression, and abnormal T-cell immune responses; which lead to B-cell hyperactivity and subsequently to the production of pathogenic autoantibodies[3]. The major organ involvement that can be associated with significant morbidity and mortality, i.e., lupus nephritis, neuropsychiatric, cardiopulmonary manifestations. Milder disease usually comprises mucocutaneous and musculoskeletal manifestations that can be treated with less-toxic treatment pathways. The treatment of moderate to severe disease comprises initially a period of intensive immunosuppressive treatment with high-dose steroids. The goal of induction therapy is to halt any ongoing systemic inflammation and to induce remission by controlling immunological activity. This is followed by less-aggressive maintenance therapy to consolidate remission and reduce the risk of flares[4].

Glucocorticoids have been used as the mainstay of treatment for SLE, with most patients undergoing long-term treatment. Glucocorticoids are associated with long-term side effects such as hypertension, diabetes, infection, and osteoporosis. As the cumulative glucocorticoid dosage increases, the rate of organ damage increases[5]. Therefore, the use of steroids should be reduced or stopped when the symptoms of lupus are controlled[4,5]. Furthermore, some previous studies have shown the possibility of steroid withdrawal in SLE patients[6,7]. A single-center retrospective study has shown that the 52-week flare rate after glucocorticoid discontinuation was 16.7%–18.2%[8]. Hypocomplementemia, elevated anti-dsDNA antibody, positive anti-Smith/anti-ribonucleoprotein antibody, and use of any immunosuppressant on the day of glucocorticoid discontinuation were negatively associated with flare-free remission, but not with the severity of organ involvement[8]. Another study, the first systematic review on this topic, included 15 cohort studies and two randomized control trials (RCT). They found a global flare incidence of 24% after glucocorticoid withdrawal. Important questions, such as the dose of prednisone before withdrawal (always lower than 10 mg/day, but only mentioned in some studies) and the time for reduction until complete withdrawal (ranging from 1 to 11 months) could not be addressed in that analysis[9]. However, few studies had specifically investigated the successful and associated factors of steroid withdrawal in systemic lupus erythematosus patients. Furthermore, research on this topic focusing on Thai patients with SLE is lacking.

Objective

Therefore, the present study was conducted to assess the success rate and associated factors of steroid withdrawal in systemic lupus erythematosus patients at Ratchaburi Hospital, Thailand.

Methods

A retrospective study based on medical records was conducted after receiving approval from the Human Research Ethics Committee of Ratchaburi Hospital (approval No. 039/2023). The study included consecutive patients with SLE who attended the outpatient unit in Ratchaburi Hospital between September 2016 and August 2020. Patients who had received steroid treatment for more than one month and had discontinued steroids were included. Patients who were under 18 years old, lacked follow-up after steroid discontinuation for one year, or had overlapping syndrome with other autoimmune diseases were excluded.

Data collection and outcome assessment

The data collected from medical records included age, gender, body mass index (BMI), duration of SLE diagnosis, age at diagnosis of SLE, anti-double stranded DNA (anti-dsDNA) status, immunosuppressive treatment on the day of glucocorticoid discontinuation, maximum dose and duration of prednisolone treatment, dose of prenisolone and time of prednisolone below 5 mg/day before discontinuation, and comorbid diseases such as hypertension, dyslipidemia, and diabetes mellitus. The diagnosis of SLE was based on the criteria of American College of Rheumatology Revised Criteria for the Classification of Systemic Lupus Erythematosus 1997 (ACR 1997)[10], Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus 2012 (SLICC 2012)[11], or European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus 2019 (ACR/EULAR 2019)[12]. Success of steroid discontinuation was defined by not resuming steroids within one year after discontinuation.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY, USA). Categorical variables, such as patients with success of steroid withdrawal, were presented as numbers with percentages and continuous variables as means with standard deviations (SDs) or medians with ranges, as appropriate. Chi-square test or Fisher's exact test were used for categorical variables and Student's t test or Mann-Whitney U test was used for continuous variables to explore the associations among factors influencing success of steroid withdrawal. The author also used logistic regression analysis to examine the factors associated with success of steroid withdrawal, with $p < .05$ as the criterion for statistical significance.

Results

At the out-patient clinic of Ratchaburi Hospital, 569 patients with SLE who were treated with glucocorticoids (all prednisolone) and followed up for more than one year between September 2016 and August 2020 were found. Of these, 200 patients (35.1%) who discontinued prednisolone were included in our study. Of the 200 patients, 175 were female (87.5%). The mean (SD) age was 42.1 (14.0) years, and 47% of them had positive serum autoantibodies against double strand deoxyribonucleic acid (anti-dsDNA). At the date of steroid discontinuation, the median SLE disease duration was 32.5 (range 1 to 278) months. The immunosuppressive treatments were azathioprine 25.5%, mycophenolate mofetil 13.5%, and methotrexate 10.1%. Almost all patients used an antimalarial drug (98.0%). Only four patients had a history of antimalarial drug allergy or intolerance side effect.

Success of steroid withdrawal in SLE patients

The overall success rate of steroid withdrawal without resuming in 1 year was 89.5% (179/200 patients). The clinical characteristics according to whether they had successful steroid withdrawal or not were reported in Table 1. Of the 21 patients who resumed corticosteroids within one year, the active organs affected by SLE at the time of resuming steroids were as follows: skin 23.8%, lupus nephritis 33.3%, arthritis 28.6%, hematologic involvement 19.0%, and other organ involvements 9.6%. The median time to resume steroids was 3 months.

Factors associated with success of steroid withdrawal

The logistic regression analysis showed that body mass index (BMI) was associated with successful steroid withdrawal (OR = 1.13, 95% CI 1.01–1.23, p = .046) relative to persons with lower BMI. The pattern of tapering prednisolone by lower 5 mg/day for more than 12 weeks before withdrawal was also associated with successful steroid withdrawal (OR = 25.44, 95% CI 8.41–76.93, p = < .001). Furthermore, antimalarial drug use at the date of steroid withdrawal was associated with successful steroid withdrawal (OR = 29.67, 95% CI 2.93–300.23, p = < .004). In contrast; age, sex, SLE disease duration, maximum dose, and duration of prednisolone usage were not significantly associated with successful steroid withdrawal; as shown in Table 2.

Discussion

Glucocorticoids have been the mainstay of treatment for systemic lupus erythematosus for more than half a century. SLE patients who receive long-term prednisone therapy are at significant risk of morbidity due to permanent organ damage or corticosteroid complications[5]. The present study reported a high rate of successful steroid withdrawal without recurrence within a year (89.5%), which was slightly above the previously reported rate (84.6%)[13]. The previous reports also showed that the percentage of SLE patients who stopped using glucocorticoids varied from 2.4% to 50.0% depending on the patients' characteristics, the organs involved

by SLE, the severity of SLE, and the use of immunosuppressive drugs[13].

The present study found some factors that were related to success, such as the use of antimalarial drugs at the time of steroid withdrawal, higher BMI, and slow reduction of steroids by decreasing prednisolone below 5 mg/day for more than 12 weeks before stopping. Regarding the antimalarial drug topic, the present study revealed that antimalarial drugs (chloroquine or hydroxychloroquine) were associated with successful steroid withdrawal with OR 29.67 (95% CI 2.93–300.23). Moroni et al.[14] also found that chloroquine lowered the risk of flare in patients who stopped glucocorticoids with concurrent treatment. These results may be explained by the fact that antimalarial agents are part of the immunomodulatory regimen

Table 1 Characteristics of the patients of systemic lupus erythematosus (SLE) according to between characteristics of patients with success and non-success steroid withdrawal

Characteristics	All participants N = 200	Success steroid withdrawal N = 179	Non-success steroid withdrawal N = 21	p-value*
Age, mean (SD), year	42.1 (14.0)	41.7 (14.2)	45.4 (12.2)	.258***
Female sex, n/N (%)	175/87.5	156/87.2	19/90.5	.714
Associated conditions				
Hypertension, n/N (%)	61/30.5	55/30.7	6/28.6	.839**
Diabetes, n/N (%)	5/2.5	5/2.8	0/0	.657
Dyslipidemia, n/N (%)	22/11	21/11.7	1/4.8	.479
Ischemic heart disease or stroke, n/N (%)	2/1	2/1.1	0/0	1.000
BMI, mean (SD), kg/m^2	23.0 (4.8)	23.2 (4.9)	21.0 (3.0)	.006***
Disease duration, median (min-max), month	32.5 (1–278)	32 (1–278)	47 (1–132)	.402†
Age at onset of SLE, mean (SD), year	38.3 (14.5)	38.02 (14.8)	41.0 (12.0)	.382***
Positivity of anti-DNA, n/N (%)	94/47	85/47.5	9/42.9	.688**
Organ involvement at steroid starting, n/N (%)				
Skin	96/48.0	86/48.0	10/47.6	.971**
Hematology	58/29.0	53/29.6	5/23.8	.580**
Lupus nephritis	77/38.5	69/38.5	8/38.1	.968**
Arthritis	73/36.5	66/36.9	7/33.3	.750**

*P-value was observed difference between characteristics of patients with CKD and without CKD by Fisher's exact test, **chi-square test, and ***Student's t test. †Mann-Whitney U test, n = the number of that condition, N = total number in the analysis, OR = odds ratio, BMI = body mass index, anti-dsDNA = anti-double stranded DNA

Table 1 Characteristics of the patients of systemic lupus erythematosus (SLE) according to between characteristics of patients with success and non-success steroid withdrawal (continued)

Characteristics	All participants N = 200	Success steroid withdrawal N = 179	Non-success steroid withdrawal N = 21	p-value*
Neuropsychiatric lupus erythematosus	13/6.5	12/6.7	1/4.8	1.000
Cardiac involvement	5/2.5	4/2.2	1/4.8	1.000
Pulmonary involvement	7/3.5	6/3.4	1/4.8	1.000
Other	5/2.5	3/1.7	2/9.5	.087
Maximum dose of steroid, median (min-max), mg	30 (5–60)	30 (5–60)	40 (10–60)	.355†
Duration of steroid, median (min–max), month	28.5 (1–278)	28 (1–278)	47 (1–132)	.639†
Prednisolone less than 5 mg/day >12 weeks before withdrawal, n/N (%)	164/82	159/88.8	5/23.8	< .001
Concomitant drug after steroid discontinuation, n/N (%)				
Azathioprine	51/25.5	46/25.7	5/23.8	.851**
Methotrexate	20/10.0	18/10.1	2/9.5	1.000
CQ or HCQ	196/98.0	178/99.4	18/85.7	.004
Mycophenolate mofetil	27/13.5	24/13.4	3/14.3	1.000
Leflunomide	2/1.0	1/0.6	1/4.8	.199
Cyclosporin	3/1.5	3/1.7	0/0	1.000
Cyclophosphamide or Chlorambucil	8/4.0	7/3.9	1/4.8	1.000

*P-value was observed difference between characteristics of patients with CKD and without CKD by Fisher's exact test, and **chi-square test, and ***Student's t test. †Mann-Whitney U test, n = the number of that condition, N = total number in the analysis, OR = odds ratio, BMI = body mass index, anti-dsDNA = anti-double stranded DNA

Table 2 Univariate logistic regression analysis of associated factors for success of steroid withdrawal in systemic lupus erythematosus (SLE) patients

Variable	Univariate model*		
	OR	95% CI	p-value
Age, year	0.98	0.95–1.01	.258
Female	0.71	0.16–3.27	.664
BMI, kg/m2	1.13	1.01–1.23	.046
SLE disease duration, month	0.99	0.99–1.01	.498
Maximum dose of steroid >30 mg/day	0.46	0.18–1.15	.096
Duration of prednisolone, month	0.99	0.99–1.01	.808
Prednisolone less than 5 mg/day >12 weeks before withdrawal, n/N (%)	25.44	8.41–76.93	< .001
CQ or HCQ	29.67	2.93–300.23	.004

*Univariate analysis was analyzed by binary logistic regression. OR = odds ratio, 95% CI = 95% confidence interval, BMI = body mass index, CQ or HCQ = chloroquine or hydroxychloroquine

used to treat patients with SLE and may help prevent lupus exacerbations[15]. In SLE patients, the role of BMI in disease activity is unclear[16]. The previous study[17] showed an association between high BMI and high disease activity in SLE. In contrast, the present study observed a relationship between successful steroid withdrawal and higher BMI. That was an interesting topic for further investigation. The present study indicated that decreasing prednisolone below 5 mg/day for more than 12 weeks before stopping was related to successful steroid withdrawal with OR 25.4 (95% CI 8.41–76.93). A previous systematic review, which including 15 cohort studies and two randomized control trials, reported a global flare rate of 24% after steroid withdrawal, which is 1.38 times higher than the rate in patients who continued steroid use[9]. In the other hand, glucocorticoid use carries a higher risk of opportunistic infections, iatrogenic osteoporosis and avascular necrosis, an increase in risk of cardiovascular events, cataracts and glaucoma, as well as psychiatric adverse effects[13]. Therefore, the 2023 EULAR SLE management guideline recommended that glucocorticoids should be reduced to maintenance dose of ≤5 mg/day (prednisone equivalent) and, if possible, stopped[18]. The present study showed the feasibility of steroid withdrawal. Furthermore; the previous meta-analysis study did not find any significant relationship between gender, disease duration, remission duration, glucocorticoid treatment duration, or the use of immunosuppressants[19];

which was consistent with the finding of the present study.

The main strength of this study was that it was the first study in Thailand to report the success and associated factors of steroid withdrawal in SLE patients. In addition, we conducted a comprehensive review of outpatient medical records from Ratchaburi Hospital, a tertiary care hospital of Thailand, which enabled us to accurately evaluate the features of the patients and the results of the treatment. This study had some potential limitations. Since this study was a retrospective medical chart review, we could not include data on possible risk factors, such as the overall disease activity of SLE before steroid withdrawal, the blood tests that may be related to disease flare such as complements[19], which were not measured or recorded in the medical charts. Furthermore, the widely ranging duration of steroid use (ranging from 1 to 278 months), strategies for steroid administration (such as intravenous pulse methylprednisolone), and a variety of steroid tapering patterns below 5 milligrams interfered with the success rate of steroid withdrawal. Because of the retrospective nature of this study, we can only draw some associations from our findings. Lastly, there was a quite small population in this study, with only 21 SLE patients who failed steroid withdrawal. Therefore, the authors did not perform a multivariate analysis to assess associated factors of steroid withdrawal success due to the small size of the population. More prospective studies are required to obtain more definitive evidence on the success of steroid withdrawal in SLE patients and its associations.

Conclusion

According to a study conducted at Ratchaburi Hospital, 89.5% of steroid withdrawal cases were successful without the need to resume steroid use in a year. The study also identified some factors that were associated with success, such as the use of antimalarial drugs at the time of steroid withdrawal, higher BMI, and slow reduction of steroids by decreasing prednisolone below 5 mg/day for more than 12 weeks before stopping. The study concluded that steroid withdrawal was feasible and the findings could be useful in planning the management of SLE.

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