Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: May 31, 2022

Citation Sankhaanuruk A, Kasitanon N, et al., 2022. Incidence of Lupus Nephritis Flares After Complete Response in a Thai Population, Medical Research Archives, [online] 10(5). https://doi.org/10.18103/mra.v10i5.2831

DOI
https://doi.org/10.18103/mra.v10i5.2831

ISSN: 2375-1924

RESEARCH ARTICLE

Incidence of Lupus Nephritis Flares After Complete Response in a Thai Population

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ABSTRACT

Background: Nowadays, we have standard treatment guidelines for lupus nephritis (LN), a substantial proportion of patients have LN flare. The aims here to determine the incidence of LN flare in patients who had renal complete remission (CR) after receiving induction therapy (IT) and to identify factors associated with renal flare after CR in clinical practice.
Methods: Retrospective analysis in a tertiary-level center for the clinical outcomes of patients who had first LN episode, achieved CR (24hr urine protein <0.5 gm/day with normal renal function) within 12 months after received IT and received the maintenance therapy (MT).
Results: Eighty-seven out of 548 patients (96.6% female with mean age 29.5±10.8 years) met the inclusion criteria. During 6.1±3.4 years of observation after CR, 42 (48.3%) patients had LN flare. The incidence ratio of LN flare was 10.9/100 patient-years. The mean time from CR to flare was 3.1 years. Using Cox-regression analysis, induction to remission therapy ≥6 months (OR=0.33, p=0.006), and using statins ≥9 months after reached CR (OR=0.44, p=0.032) had a lower incidence of LN flare, while age at onset of disease ≤20 years had a higher incidence of LN flare.
Conclusion: Despite achieving CR with standard treatment, almost half of the patients had an LN flare within a few years. Young SLE patients had an increased incidence of LN flare, the long period of induction therapy and using statins may retard a flare of the disease.

Keywords: Lupus nephritis, Maintenance phase, flare, risk factors

Introduction

The systemic lupus erythematosus (SLE) is an autoimmune disease mainly found in reproductive women, typically involving multi-organ systems. The prevalence of lupus nephritis (LN) varies across ethnicities. A previous systematic review found a higher prevalence in Asians with more renal involvement than that found in Caucasians[1]. In Thailand, LN was observed during SLE diagnosis in 53 %, and 78 % of patients the disease[2]. Also, the response rate to the treatment of LN varies among ethnicities.[3,4]

The clinical course of LN is typically characterized by periods of remission and flare[5]. After stopping immunosuppressive drugs, a substantial proportion of SLE patients have an LN flare, ranging in different studies from 27% to 66%[6]. A flare of LN results in increased risk of end-stage kidney disease (hazard ratio 3 – 13.6).[7,8] Nephron loss from each LN flare compounds nephron loss from earlier flares and ageing, further shortening kidney lifespan.[9] In addition, a flare of LN, also, increased risk of patients exposed to high doses of corticosteroid and immunosuppressive drugs from re-induction therapy. A study from the National Institutes of Health (NIH) showed that patients treated with short-course cyclophosphamide had a higher probability of exacerbations (15.6/100 patients-year) than those treated with long-course cyclophosphamide (2.4/100 patients-years)[10]. Therefore, standard treatment guidelines to prevent LN flare[11] recommend maintenance therapy after LN reaches complete remission (CR).

The objective of this study was to determine: the incidence of LN flare in Thai patients who reached renal CR after receiving induction therapy; the time from CR to flare; and to identify associated factors for LN flare in a clinical practice setting. Complications during maintenance therapy were also examined.

Patients and Methods

Study Design and Population

The medical records of SLE patients who were followed up at the Division of Rheumatology, Chiang Mai University between January 1, 1997, and June 30, 2016, were evaluated. This study included SLE patients with an age of onset more than 15 years-old, met American College of Rheumatology (ACR) Classification Criteria for SLE[12], had the first episode of LN, met CR of LN criteria within 1 year after start induction therapy and remained in the cohort for maintenance therapy for at least 18 months after CR. We excluded patients with overlap syndrome.

Data collection

The following data were verified via manual review of medical records: diagnostic criteria, LN manifestation since patients were diagnosed, laboratory data, modified Systemic Lupus Erythematosus Disease Activity Index 2000 (mSLEDAI-2K)[13], Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index for SLE (SLICC/ ACR DI)[14] at the time when patients met CR criteria. Therapeutic management, blood pressure, complete blood counts, urine analysis, serum albumin and serum creatinine, erythrocyte sedimentation rate (ESR), urine sediment and medications (prednisolone, immunosuppressive drugs, an anti-malarial drug, Angiotensin-Converting Enzyme Inhibitor (ACEI), and statins) were recorded every 1-3 months after patients met CR criteria, depending on other lupus clinical manifestations. In those who had LN, 24-hour urine protein and creatinine collection were routinely performed every visit during active LN, and at least every three months after the patients had complete renal remission.

Definition

Lupus nephritis was defined as patients with proteinuria ≥ 0.5 gm at 24 hours urine collection or urine protein creatinine index or pathology diagnosed from kidney biopsy. CR was considered when LN patients had proteinuria ≤ 0.5 gm/ day and serum creatinine ≤ 1.2 mg/ dl. A renal flare was defined as proteinuric flare when there was the recurrence of the development of nephrotic syndrome; or for patients with low-grade baseline 24- hours urine protein (≥ 0.5 and < 1 g)—a threefold increase of 24 hours urine protein within 3 months LN[13].

Severe adverse events consisted of the following: discontinued immunosuppressive drugs, hospital admission, opportunistic infection, or morbidity from therapy.

Statistical analysis

The statistical analyses were performed using the Statistical Package for Social Sciences Software (SPSS Inc, Chicago, IL), version 17.0, for Windows XP. For the comparison between patients with and without renal flare, the unpaired Student t-test was used for continuous data. The log-rank test was used for categorical data. The variables

with a p-value of ≤ 0.15 were selected for multivariable analysis. Cox regression analysis was used to observe independent risk factors for renal flare. For all statistical evaluations, P ≤ 0.05 was considered statistically significant.

Results

Among 548 patients in the medical record database, 171 patients who had the first episode of LN were identified. Of 171 patients, 87 patients met the inclusion criteria, while 84 patients were excluded due to failure to reach CR within one year (n=64) and on maintenance therapy for less than 12 months (n=20).

Most of the cases were women (96.6%). Their mean age was 29.5 ± 10.8 years. The other baseline characteristics are listed in Table 1. Induction therapy with cyclophosphamide was administered in 63 (72.5 %) patients, mycophenolate mofetil (MMF) in 12 (13.8 %) patients, azathioprine in five (5.7%) patients, and others in seven (8.0 %) patients. The number of patients who reached CR within 6, 9 and 12 months was 61 (70.1 %), 18 (20.7 %) and 8 (9.2 %), respectively. The mean duration of induction therapy was 6.4 ± 2.7 months. At maintenance therapy initiation, the mean of 24-urine protein was 0.37 ± 0.38 mg/ day and the mean of prednisolone was 9.1 ± 5.1 mg/ day.

Lupus Nephritis Flare

After reached CR, the maintenance therapy was azathioprine in 45 (51.8 %) patients, MMF in 19 (21.8 %) patients, cyclophosphamide in 9 (10.4 %) patients, cyclosporine A in one (1.1 %) patient and no immunosuppressant in 13 (14.9 %) patients. The mean duration of immunosuppressant treatment was 25.9 ± 10.4 months.

During 6.1 ± 3.4 years of the observation period after patients reached CR, 42 out of 87 (48.27 %) patients had an LN flare. Therefore, the incidence rate of LN flare was 10.9/ 100 patient-years. The mean time from CR to LN flare was 3.14 (min 0.5, max 9.5, median 2.5) years as shown in Figure 1. There were no differences in baseline characteristics between patients with and without LN flare as shown in Table1. Forty-six patients (57.9%) received maintenance therapy more than 18 months. When compared between patients with maintenance therapy more than 18 months and less than 18 months, patients with maintenance therapy more than 18 months had significant lower proportion of LN flare (37.0% vs. 61.0%, p = 0.032). There was no difference in extra-renal manifestations between patients who had LN and who had no LN flare.

Figure 1 Survival of complete remission in lupus nephritis

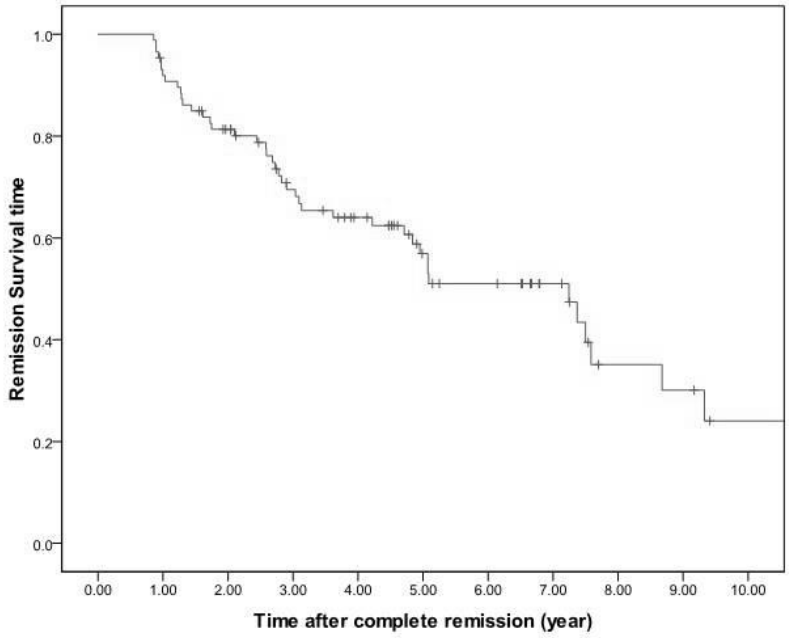

Table 1: Characteristics of patients

characteristics	Total 87 (100)	No Flare, N (%) 45 (51.7)	Flare, N (%) 42 (48.3)	P-value
Age at onset SLE* (years)	29.5 ± 10.8	31.12 ± 11.33	27.74 ± 9.97	0.144
Age at LN* (years)	32.8 ± 11.3	35.05 ± 12.08	30.42 ± 10.05	0.057
UPCI at initiated IT*	2.87 ± 2.83	2.49 ± 1.81	3.23 ± 3.52	0.229
UPCI at initiated MT*	0.37 ± 0.38	0.40 ± 0.43	0.33 ± 0.33	0.383
Serum creatinine* (mg/ dl)	0.92 ± 0.47	0.88 ± 0.24	0.96 ± 0.63	0.571
Prednisolone*, **(mg/ day)	9.11 ± 5.06	9.78 ± 6.21	8.39 ± 3.35	0.204
Antimalarial drug	44 (50.6)	22 (50.0)	22 (50.0)	0.831
ACEI**	44 (50.6)	22 (50.0)	22 (50.0)	0.108
Statins**	38 (43.7)	22 (57.9)	16 (42.1)	0.388
Duration of IT (months)	5.29 ± 2.99	6.67 ± 3.15	4.45 ± 2.59	0.011
Drugs for induction therapy				
Cy	63 (72.5)	31 (49.2)	32 (50.8)	0.481
AZA	5 (5.7)	4 (80.0)	1 (20.0)	0.362
MMF	12 (13.8)	6 (50.0)	6 (50.0)	1.00
Others	7 (8.0)	4 (57.1)	3 (42.9)	1.00
Drugs for maintenance treatment				
Cy	9 (10.3)	4 (44.4)	5 (55.3)	0.612
AZA	45 (51.7)	24 (53.3)	21 (46.7)	0.909
MMF	19 (21.8)	11 (57.9)	8 (42.1)	0.571
Others	14 (16.1)	6 (42.9)	8 (57.1)	0.868
MT > 18 months	46 (57.9)	29 (63.0)	17 (37.0)	0.032

* = mean±SD, **at initiate maintenance treatment, LN lupus nephritis, UPCI urine protein creatinine ratio, IT induction therapy, MT maintenance treatment, CR complete remission, ACEI Angiotensin-converting enzyme inhibitors

Associated factors of lupus nephritis flare

A log-rank test was used to identify associated risk factors of LN flare. We compared the following basic characteristics: 24-hour urine protein at initiated induction therapy, renal variables and medications (prednisolone, immunosuppressive drugs, anti-malarial drugs, ACEI, and statins) at 3, 6, 9, 12, 15 and 18 months after initiated maintenance therapy. The following factors were analyzed using Cox-regression: age at onset of disease, induction therapy with MMF, time of induction to CR ≥ 6 months, stayed on prednisolone ≥ 7.5 mg/ day during the first three months of maintenance therapy and used statins ≥ 9 months after reaching CR, had trended to be associated with a flare of LN (p-value ≤ 0.15).

For the multivariate Cox-regression analysis, time of induction to CR ≥ 6 months (OR = 0.33, p = 0.006), and used statins ≥ 9 months after reaching CR (OR = 0.44, p = 0.032) had a lower incidence of LN flare, while age at onset of disease ≤ 20 years had a higher incidence of LN flare (**Table 2**). Other demographic characteristics, clinical variables, and other treatment variables were not associated with the incidence of LN flare.

Table 2: Risk factors of lupus nephritis flare

Variables	Cox regression analysis		
	HR	95% CI	*p-value*
Age at onset ≤ 20 years	2.30	1.08 – 4.89	0.031
Induction therapy with MMF	2.04	0.78 – 5.30	0.145
Induction treatment ≥ 6 months	0.33	0.15 – 0.73	0.006
Using statins longer than 9 months	0.44	0.21 – 0.93	0.032
On prednisolone ≥ 7.5 mg/ day during the first 3	0.51	0.23 – 1.11	0.091

MMF mycophenolate mofetil, UPCI urine protein creatinine ratio, CR complete remission, mg milligram, HR hazard ratio, CI confident interval

Adverse events

During maintenance therapy, 15 patients (17.2 %) had severe adverse events. The most common cause was severe infection in 9 (60.0%) patients including 3 cases of Pneumocystis jiroveci pneumonia (PCP), 2 cases of herpes zoster, 1 brain abscess, 1 case of pneumonia, 1 peri-anal abscess, and 1 disseminated strongyloidosis. Five (33.3 %) of these patients had to stop maintenance therapy due to severe infection. The other severe adverse events were leukopenia in 3 patients, transaminitis in 2 patients and avascular necrosis of the hip in 1 patient.

Discussion

Maintenance therapy for LN patients who reached CR is justified by the relapsing nature of LN, because frequent relapses lead to progressive deterioration of renal function[7,16]. However, in general practice a substantial proportion of patients had LN flare, even though the patients followed the current standard treatment of LN with induction therapy and subsequent maintenance therapy. Focusing on maintenance therapy for LN, although, in this study, patients with their first LN episode who reached CR after receiving induction therapy, the incidence of LN flare was approximately 50% of patients within three years after CR. This data is compatible with studies from other countries where the incidence of LN flare ranged from 27 – 66 %[6].

Although maintenance therapy is well accepted for LN, many details of these treatments are not well-defined. For example, the varying doses and duration of immunosuppressive drugs and corticosteroids or adjunctive treatment are adjusted according to individual patient characteristics. Therefore, characterizing risk factors such as LN flares allow physicians to improve outcome prediction resulting in better patient care.

For dose of steroid in LN, according to expert opinion, the 2019 European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommended prednisone tapered to 7.5 mg daily by 3 to 6 months after induction therapy.[11] However, in this study, prednisolone ≥ 7.5 mg/ day during the first three months of maintenance therapy had a trend to reduce the incidence of LN flare from univariable analysis but had no significant difference in multivariable analysis. Therefore, the proper dose and duration of corticosteroids must balance benefits and risks.

To prevent LN flare, standard treatment guidelines recommend maintenance therapy after LN reaches complete remission. The results from this study supported the longer maintenance therapy, the lower incidence of LN flare. The 2019 EULAR/ERA-EDTA) recommendations gradual withdrawal of immunosuppressive drugs can be attempted after at least 3 to 5 years therapy in complete clinical response.[11] The wide range of recommended maintenance duration, may due to insufficient evidence available regarding the best target of nephritis responses, clinical, pathology or other biomarker response, which indicate true remission in LN.

For type of immunosuppressive drugs and incidence of LN flare, in the induction phase, this observational study had no difference in the incidence of LN flare across immunosuppressive drugs during induction therapy. These results supported a previous clinical trial that reported no difference in LN flare between patients who received MMF and those who received cyclophosphamide for induction therapy.[17] However, we found that the duration of induction is crucial. Patients who received induction therapy ≥ 6 months had less incidence of LN flare. The reason that patients who received longer induction therapy, which seem to have more severity of proteinuria, had a lesser incidence of LN flare may due to the longer immune suppression period had longer able to prevent flare of the disease. This result is consistent with a previous study by Moroni G et al[17] that found, after remission, LN patients without flare had significantly longer induction therapy duration than LN patients who experienced a new flare. Therefore, regarding the flare rate after remission, our data support the recommendation that the duration for the induction therapy should be at least six months.

During maintenance therapy, there was no difference in the incidence of LN flare across immunosuppressive drugs. This result was consistent with a recent meta-analysis of seven randomized controlled trials that compared the maintenance regimens of mycophenolate mofetil and azathioprine in the treatment of LN and found no difference in flare rate and other outcomes e.g. mortality, end-stage renal disease, doubling of serum creatinine, and adverse effects, between mycophenolate mofetil and azathioprine.[18] It should be noted that in clinical practice, physicians may allocate immunosuppressive drugs according to many factors e.g. age, disease severity, infection,

co-morbidities, or economic status etc. Therefore, in this observation, physician judgment may affect drug regimens and few patients in each regimen could not reach power to detect the difference.

The results demonstrate that patients who received statins ≥ 9 months after reached CR had lower incidence of LN flare. Recently, statins are ratified effective in the primary prevention of cardiovascular disease in patients with SLE.[19] For SLE patients with LN, there was some evidences that statins also diminish SLE activity. A previous study in mice found that statins have effects on endothelial cells and B cells, as well as reducing levels of ds DNA antibodies and proteinuria.[20] Besides, a small open-label study assessed the effect of statins therapy for one year in 12 patients with refractory LN and found creatinine clearance maintained stability, while proteinuria, prednisone dose, and relapses decreased during the year after the initiation of statins.[21] Therefore, we proposed the use of statins after remission of LN may prevent subsequent flare of LN in the long term. However, the role of statins to prevent LN flare and proper duration need more studies before a recommendation can be made.

For the baseline characteristics, SLE patients with an onset of SLE disease less than 20 years old had a higher incidence of LN flare. Previous studies demonstrated that patients who had the early age of SLE onset (≤ 18 years old) had more prevalence of LN[22,23], had more severe LN[24,25], and had more risk incidents of end state renal disease[26] than adult-onset and late-onset of SLE. This study supported evidence that early age of onset SLE patients had a poor prognosis of LN, therefore regular monitoring of urine protein levels is crucial particularly for patients with age of disease onset less than 20 years old.

It should be noted that the renal pathology of LN is not available due to it is an observational study that collected data from real clinical practice. In our cohort, we did not do a renal biopsy in all patients. Also, some factors in this study were not precisely controlled. Particularly, type, dose and duration of drug assignment depended on physician judgment in a real-world clinical setting. However, despite these variable conditions, we observed each patient for at least 18 months after CR, which is long enough to observe LN flare. Also, our study identified factors associated with LN flare by using a specific and appropriate time-to-event analysis.

In conclusion, despite achieving CR with standard treatment, nearly half of the patients in this study had LN flare within a few years. This study emphasizes that adequate induction therapy for at least six months and maintenance therapy more than eighteen months are essential for long-term treatment outcomes and although immunosuppressive agents are effective, adjunctive therapy as statins may help to reduce the incidence of LN flare. Further studies aimed at identifying predictive factors of disease quiescence after drug discontinuation are needed.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare

Funding Statement

This work was supported by the Division of Rheumatology and Faculty of Medicine, Chiang Mai University (053/ 2559).

Disclosure Statement

The authors declared no conflicts of interest.

Compliance with Ethical Standards

The study was conducted according to the Declaration of Helsinki, and was approved by the Ethics Committee of the Faculty of Medicine at Chiang Mai University.

Acknowledgments

The authors thank Dr. Antika Wongthanee for statistical assistance and Dr Elizabeth Matovinovic for manuscript editing.

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