Original Article

Incidence Rate, Causes and Predictors of Opportunistic Infection during High-Dose Steroid with and without Immunosuppressant Therapy in Thais with Systemic Lupus Erythematosus

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Objective: Our aims were to define the incidence rate and predictors of opportunistic infection (OI) in systemic lupus erythematosus (SLE) patients.

Materials and Methods: A historical cohort study was conducted on patients over 15 years of age diagnosed with SLE, who attended the out-patient clinic or were admitted to Srinagarind Hospital, Khon Kaen, Thailand, between January 1, 2009 and December 31, 2014.

Results: The medical records of 132 SLE patients were reviewed. The female to male ratio was 13:1. Among the total 713.9 person-years, 6 cases had OI during follow-up with an incidence rate of 0.7 per 100 person-years (95% CI 0.9 to 1.7). Three of the cases received high-dose steroid with or without immunosuppressant for an incidence of 0.42 per 100 person-years (95% CI 0.13 to 1.30) and three had no high-dose steroid treatment during OI detection for an OI incidence of 0.28 per 100 person-years (95% CI 0.07 to 1.12). Pulmonary nocardiosis was the most common OI (4 cases; 66.7%), followed by disseminated candidiasis (1 case; 16.7%), and cryptococcal meningitis (1 case; 16.7%). Full recovery of OI occurred in 3 of 4 of with pulmonary nocardiosis and in 1 with cryptococcal meningitis, while one with pulmonary nocardiosis and one with disseminated candidiasis died at 33 and 6 days after OI, respectively.

Conclusion: The occurrence of OI in SLE is not common. Pulmonary nocardiosis was the most common OI, and all received moderate to high dose with and without immunosuppressant.

Keywords: Systemic lupus erythematosus; Infection; Opportunistic infection; Incidence rate

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Systemic lupus erythematosus (SLE) is a serious autoimmune disease occurring most commonly in women[1-3]. The disease may cause organ inflammation and permanent structural damage. Some patients die because of the severity of the disease and related infections so that the death rate among SLE patients is between 4.5 and 24%[2-8].

The causes of death among SLE patients have a bimodal distribution; infection being the most common cause in the first 5 years after diagnosis followed by coronary artery disease in later years[2]. Infection, however, is the major persistent cause of mortality irrespective of age. Gram negative bacterial and opportunistic infections (OI) are serious in SLE patients[5-12].

Infections—particularly OI such as cryptococcosis and invasive aspergillosis—are not uncommon among SLE patients[13,14]. OI occur in our daily practice in patients who receive high-dose steroid therapy with or without immunosuppressant and these infections are a major cause of death in SLE patients[2,5-13]. There are reports on the incidence and causes of OI among SLE patients[14]. Our center is tertiary center and is in an endemic area for some infections including tuberculosis, cryptococcosis, and aspergillosis. The study objectives were (a) to estimate the incidence of infection (b) to determine the cause(s) of infection especially OI; and (c) to evaluate the predictors of OI during high-dose steroid with or without immunosuppressant therapy in Thai SLE patients. Once the predictors of OI are identified, the risks could be addressed and/or prevented.

Materials and Methods

The authors conducted a historical cohort study

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on SLE patients over 15 years of age, diagnosed with SLE per the criteria of the American College of Rheumatology (ACR). The patients were followed-up at the Out-patient Clinic or hospitalized at Srinagarind Hospital, Khon Kaen University, Thailand, between January 1, 2009 and December 31, 2014. Patients who had overlap with other connective tissue diseases were excluded except for those with anti-phospholipid syndrome.

Operational definition

The beginning date was at the time of SLE diagnosis. If the patient were diagnosed with SLE before being referred to our hospital, the date of SLE diagnosis at the local hospital was entered as the beginning date. The end date was the infection date if the patient was diagnosed as having an infection; otherwise it was the last follow-up if the patient were lost to follow-up or the patient still had no infection at the end of the study period. Time to event (infection) was calculated by subtracting the end date from the date at SLE diagnosis. Disease duration was the time between disease onset and the end of follow-up. The definition of low-, moderate-, and high-dose steroid use during OI was fulfilled when the patient received a steroid equivalent of <15 mg, 15 to 30 mg, and >30 mg prednisolone/day within 2 weeks of OI. The definition of immunosuppressant use during OI was fulfilled when the patient received any immunosuppressive agent within 2 weeks before OI. Minor organ involvement included constitutional symptoms, skin involvement, musculoskeletal involvement, or serositis that did not need moderate to high-dose steroid or immunosuppressant treatment. Major organ involvement was fulfilled if the patient needed at least moderate-dose steroid and/or immunosuppressant.

The definition for infection was evidence of infection confirmed by documents from the Microbiology Unit and a specialist in infectious diseases or a rheumatologist. OI is an infection caused by an unusual pathogen infection (i.e., Nocardiosis, invasive aspergillosis, systemic candidiasis, cryptococcosis, *Pneumocystis jiroveci*, or cytomegalovirus) in a host with a normally functioning immune system.

Statistical analysis

The incidence rate with 95% confidence interval and median time of OI was calculated. The hazard ratio (HR) and cox regression were calculated to assess the risk of infection. A p-value <0.05 was considered statistically significant. All of the data analyses were performed using STATA version 16.0 (StataCorp Inc., College Station, TX, USA).

Results

The medical records of 132 SLE patients were reviewed. Female patients presented more frequently than male (123 vs. 9 cases). The respective mean age at onset of SLE diagnosed and median duration of disease was 28±11 years and 6.3 years (interquartile range (IQR) 1.7 to 8.5). Of the total 713.9 person-years, 6 cases had OI during follow-up for an incidence rate of 0.7 per 100 person-years (95% CI 0.9 to 1.7).

Five patients with OI received high-dose steroid with and without immunosuppressant for an incidence of 0.56 per 100 person-years (95% CI 0.20 to 1.49) while 1 case had no high-dose steroid treatment during OI detection for an incidence of OI of 0.14 per 100 person-years (95% CI 0.02 to 0.99).

Pulmonary nocardiosis was the most common OI (4 cases; 66.7%), followed by disseminated candidiasis (1 case; 16.7%) and cryptococcal meningitis (1 case; 16.7%). The outcome of OI was 'fully recovered' in 3 of the 4 patients with pulmonary nocardiosis and the one with cryptococcal meningitis whereas one with pulmonary nocardiosis and one with disseminated candidiasis died 33 and 6 days after OI, respectively.

The clinical characteristics and outcome of patients with OI are presented in Table 1.

The clinical comparison between the patients with OI vs. no OI revealed that dyslipidemia was the only clinical parameter that increased the risk of OI in SLE patients HR of 17.75 (95% CI 1.10 to 285.64) whereas other clinical parameters—such as sex, age, and organ involvement—were not associated with OI. The clinical difference between SLE with and without OI are presented in Table 2.

Discussion

SLE patients are more susceptible to infection than the general population. This may be due to impaired phagocytosis, defects in chemotaxis, abnormal complement levels, decreased immune complex clearance, and/or mutations in mannose-binding lectin and Fc receptors[15]. Exposure to immunosuppressants—such as mycofenolate mofetil, cyclophosphamide, and azathioprine—may prolong the effect on the immune system. These factors may make SLE patients more susceptible to OI.

The occurrence of OI among Thai patients with SLE is not common; however, the infection can occur in those who received low- to moderate-dose steroid 2 weeks prior OI. The most common OI in our study was pulmonary nocardiosis. Unfortunately, there is no way to screen and/or provide prophylaxis for *Nocardia* spp. infection in SLE patients. The rational use of antibiotic prophylaxis of the infection is limited. By contrast, with *Pneumocystis jiroveci* there is strong evidence for use of antibiotic prophylaxis—co-trimoxazole—in patients who need prednisone ≥20 mg/d or equivalent for one month or longer[16,17]. Co-trimoxazole was prescribed for most of our patients who received high-dose steroid or immunosuppressant (data not shown), so there was no *Pneumocystis jiroveci* reported among our SLE patients. Although, pulmonary nocardiosis was detected as the most common OI pathogen, the prognosis was not bad. Only 1 case was died as a result of a nocardiosis infection, whereas the others fully recovered after OI treatment. We thus suggest that in SLE patients receiving moderate-dose steroid treatment, antibiotic prophylaxis for nocardiosis remains uncertain because of limited evidence.

Table 1. Clinical characteristics of patients with OI

Data	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Sex	Female	Female	Female	Female	Male	Female
Age at onset (years)	55.7	40.2	16.5	33.3	19.6	20.9
Age at OI diagnosis (years)	56.0	46.1	20.6	39.2	24.6	40.7
Duration of disease at OI diagnosis (years)	0.3	5.9	4.1	5.9	6.0	19.8
Clinicals of SLE two weeks before OI						
Minor organ involvement	-	AIHA, Leukopenia, Arthritis, Serositis			Serositis	-
Major organ involvement	-	LN class V	LN class III	LN class III		- -
Comorbid disease	-	HT	DM, HT	DM, HT, DLD	-	-
Treatment (2 weeks before OI)						
Steroid (mg/day)	30	40	30	10	30	30
Immunosuppressant	-	Cyclophosphamide	MMF	MMF	-	Azathioprine
Opportunistic infection site	Lung	Lung	Lung and GI	CNS	Lung	Lung
Pathogen	Norcardia	Norcardia	Candida	Cryptococcus	Norcardia	Norcardia
Outcome	Death	Fully recovery	Death	Fully recovery	Fully recovery	Fully recovery

OI = opportunistic infection; SLE = systemic lupus erythematosus; AIHA = autoimmune hemolytic anemia; LN = lupus nephritis; DM = diabetes mellitus; HT = hypertension; DLD = Dyslipidemia; CNS = central nervous system; GI = Gastrointestinal; MMF = Mycophenolate mofetil

Table 2. Clinical difference between SLE with and without OI

Clinical parameter	No infection n=126 (%)	OI n=6 (%)	Hazard ratio (95% CI)	p-value
Sex				
Male	8 (6.3)	1 (16.7)	NA	NA
Female	118 (93.7)	5 (83.3)	NA	NA
Age at onset of disease (years); mean±SD	28.3±11.6	22.1±8.1	1.02 (0.9 to 1.1)	0.7
Clinical presentation at onset infection				
General symptoms	12 (9.4)	2 (50.0)	8.8 (0.7 to 113.1)	0.10
Musculoskeletal symptoms	0	0 (0.0)	NA	NA
Skin	2 (1.6)	0 (0.0)	NA	NA
Hematological symptoms	5 (3.9)	1 (25.0)	3.8 (0.2 to 99.5)	0.43
Neurological symptoms	0	0	NA	NA
Gastrointestinal symptoms	0	0	NA	NA
Cardiopulmonary symptoms	2 (1.6)	1 (25.0)	2.7 (0.1 to 54.6)	0.51
Lupus nephritis	5 (3.9)	1 (25.0)	2.7 (0.1 to 54.6)	0.51
Leukopenia	2 (1.6)	1 (25.0)	4.4 (0.1 to 141.7)	0.40
Hypoalbuminemia	2.9±1.1	2.5±0.8	0.9 (0.2 to 3.5)	0.91
Co-morbidity at onset infection				
Diabetes mellitus	3 (2.3)	2 (50.0)	NA	NA
Hypertension	6 (4.7)	3 (75.0)	NA	NA
Dyslipidemia	4 (3.1)	1 (25.0)	17.8 (1.1 to 285.6)	0.04*
Cardiovascular disease	0	0	NA	NA
Hepatitis B and/or Hepatitis C infection	0	0	NA	NA
Antiphospholipid syndrome	2 (1.6)	0	NA	NA

* Statistical significant
OI = opportunistic infections; SD = standard deviation

Four of our patients with OI received immunosuppressants—including cyclophosphamide, mycophenolate mofetil, and azathioprine. Mycophenolate mofetil was prescribed for treatment of LN class III in 2 of our SLE patients and both had coexisting diabetes mellitus: one had a disseminated fungal infection and one cryptococcal meningitis. Both of these patients were undergoing cyclophosphamide and azathioprine treatment and had pulmonary nocardiosis. The SLE patients treated with mycophenolate mofetil, cyclophosphamide, or azathioprine were at risk of OI; however, due to low numbers of OI in our study, the statistical power was too low to identify the magnitude of risk of OI among those receiving immunosuppressant therapy. A longitudinal study using a database for the USA revealed that the rate of serious infection and mortality—in new users of cyclophosphamide, mycophenolate mofetil, or azathioprine—were not different[18]. The findings reveal that all SLE patients should be evaluated for occult infection and evaluated for risk of infection irrespective of which immunosuppressants being used for disease control.

Invasive fungal infection results in a high mortality rate in SLE patients undergoing steroid and immunosuppressant treatment. In the current study, one patient died due to disseminated candidiasis. The patient with diabetes mellitus as a coexisting disease received prednisolone (30 mg/d) with mycophenolate mofetil 2 weeks prior to OI detection. Once an invasive fungal infection is detected in a patient SLE undergoing immunosuppressant therapy, high morbidity and mortality are a real concern.

In the current study, dyslipidemia was a comorbid disease that increased the risk of OI in SLE patients during high-dose steroid treatment with and without immunosuppressant, while other atherosclerotic diseases—such as diabetes mellitus, hypertension or cardiovascular disease—did not result in the same increase. The reason for the finding is uncertain, and could be due to chance, so a study in a large population should be done.

Our study had some limitations due to (i) the small number of SLE patients with OI, resulting in a low statistical power; (ii) missing data due to the nature of retrospective

data collection; (iii) the causative organism not being identified in some cases, so we could not conclude whether or not it was OI; and, (iv) not using the Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC) for SLE diagnosis because the patients were included before the classification criteria was launched. Notwithstanding, the preliminary data provides information for better care of SLE patients vis-a-vis the awareness, monitoring, and prevention of OI among SLE patients undergoing/not undergoing high-dose steroid treatment.

Conclusion

The incidence of OI in SLE is not common. Pulmonary nocardiosis was the most common OI and all received moderate to high dose steroid with and without immunosuppressant.

What is already known on this topic?

The causes of death among SLE patients have a bimodal distribution; infection being the most common cause in the first 5 years after diagnosis. Infection is the major persistent cause of mortality irrespective of age particularly gram negative bacterial and opportunistic infections.

What this study adds?

The incidence of OI in SLE is not common. Pulmonary nocardiosis was the most common OI and all received moderate to high dose steroid with and without immunosuppressant.

Ethics approval

The Human Research Ethics Committee of Khon Kaen University reviewed and approved the study per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE581158).

Consent for publication

The authors consent to publication and grant the publisher exclusive license of the full copyright.

Availability of data and material

Data or materials available on request.

Competing interests

The authors have no competing interests.

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Author's contributions

PK collected the data and drafted the manuscript. CF and SS conceived and designed the study. CF, SS, AM, SN and RN read and commented on the manuscript.

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Potential conflicts of interest

The authors declare no conflict of interest.

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