

Varicella zoster virus infections increase the risk of disease flares in patients with SLE: a matched cohort study

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ABSTRACT

Objective To explore whether varicella zoster virus (VZV) infection could increase the risk of disease flares in patients with SLE.

Methods Patients who had VZV reactivations between January 2013 and April 2018 were included from the SLE database (n=1901) of Shanghai Ren Ji Hospital, South Campus. Matched patients with SLE were selected as background controls with a 3:1 ratio. Patients with SLE with symptomatic bacterial infections of the lower urinary tract (UTI) were identified as infection controls. Baseline period and index period were defined as 3 months before and after infection event, respectively. Control period was the following 3 months after the index period. Flare was defined by SELENA SLEDAI Flare Index. Kaplan-Meier analysis, Cox regression model and propensity score weighting were applied.

Results Patients with VZV infections (n=47), UTI controls (n=28) and matched SLE background controls (n=141) were included. 16 flares (34%) in the VZV group within the index period were observed, as opposed to only 7.1% in UTI controls and 9.9% in background controls. Kaplan-Meier curve revealed that patients with a VZV infection had a much lower flare-free survival within the index period compared with the controls (p=0.0003). Furthermore, after adjusting for relevant confounders including baseline disease activity and intensity of immunosuppressive therapy, Cox regression analysis and propensity score weighting confirmed that VZV infection within 3 months was an independent risk factor for SLE flares (HR 3.70 and HR 4.16, respectively).

Conclusions In patients with SLE, recent VZV infection within 3 months was associated with increased risk of disease flares.

INTRODUCTION

SLE is a chronic multisystem autoimmune disorder which typically manifests in a relapsing-remitting pattern. However, the cause or trigger and the underlying mechanism of flares are complex and largely undetermined, which makes clinical prediction of flare very difficult. Viral infections have been implicated as contributing factors to the onset and flare-up of SLE. For example, Epstein-Barr

virus was reported as a trigger for SLE and other autoimmune diseases.¹ Cytomegalovirus infection may also precipitate SLE flare.² Likewise, acute parvovirus B19 infection that antedated a serious episode of SLE flare has been anecdotally reported.³ It is postulated that viral infection may lead to memory T-cell proliferation and overproduction of interferons, which in turn are a major player in lupus pathogenesis.⁴ Varicella zoster virus (VZV) reactivation is common in SLE, with an incidence of 6.4–32.5 per 1000 person-years, significantly higher than 1.5–3.0 per 1000 person-years as reported in the general population.⁵ Patients with active SLE who need more intensive immunosuppressive (IS) therapy were more predisposed to VZV infections.^{5,6} However, mild or even inactive patients could also have VZV infections, and they account for about two-thirds of the events.^{5–7} A case-control study has described that there was close association between VZV reactivation and SLE diagnosis.⁸ Whether the infection of VZV could increase the risk of disease flares in patients with SLE was unclear. We aimed to address this question in our cohort.

METHODS

We conducted this retrospective cohort study in a single centre, Shanghai Ren Ji Hospital, South Campus. Patients who had infections of non-disseminated VZV between January 2013 and April 2018 were included from our SLE database (n=1901). Patients with SLE who visited at the same time as each patient with VZV event were selected as background controls with a 3:1 ratio. Additionally, patients with SLE with symptomatic bacterial infections of the lower urinary tract (UTI) were enrolled as infection controls, who had pyuria with either positive results on microbiological analysis or a good response to antibiotics.

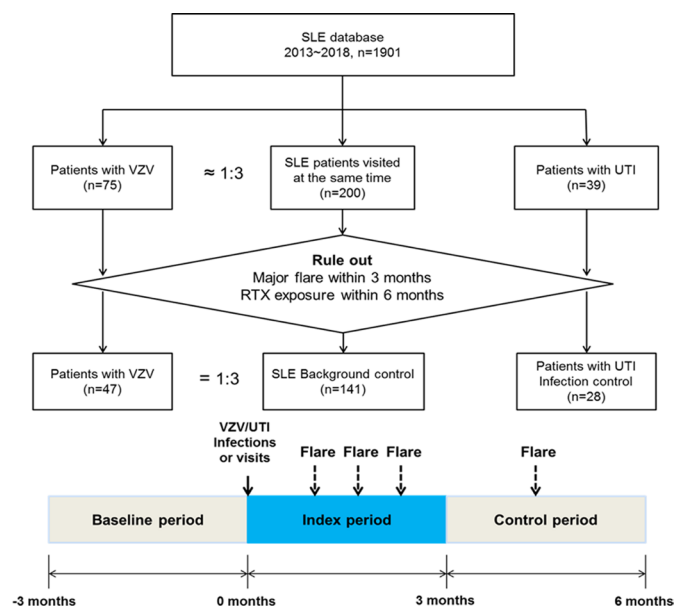


Figure 1 Flow chart and schematic of the study. RTX, Rituximab; UTI, bacterial infections of the lower urinary tract; VZV, varicella zoster virus.

All patients had regular follow-up records at an interval of 1–3 months during the study period. Medical data including age, gender, disease duration, disease activity evaluated by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and cumulative organ involvement counted as the number of eight domains (mucocutaneous, neurological, musculoskeletal, cardiovascular/respiratory, vasculitis, renal, haematological and ophthalmic diseases) in the British Isles Lupus Assessment Group 2004 index were collected. Baseline period and index period were defined as 3 months before and after infections or visits, respectively. The control period was three consecutive months following the index period (figure 1). In order to reduce the effects of baseline high disease activity and intense IS therapy on the subsequent disease flares in the index period, we excluded patients with major flares within the baseline period. Patients who have been exposed to rituximab within 6 months before infections or visits were also excluded. Daily prednisone, hydroxychloroquine (HCQ) and IS agents were recorded during the baseline and index periods. Flare was defined by the SELINA SLEDAI Flare Index (SFI). Clinical data were expressed as mean±SD. Variables were compared using the Mann-Whitney U test or χ^2 test. Flare-free survival was assessed by Kaplan-Meier curve. Cox regression analysis was performed to identify the risk factors of flare. Inverse probability treatment weighting of propensity score model was applied to balance the covariates between groups, especially disease activity and previous IS therapy. All statistical analyses were conducted in GraphPad V.5.0 or SPSS V.22.0 software package. $P < 0.05$ was considered statistically significant.

RESULTS

We identified 47 patients with VZV reactivations and 141 matched SLE background controls (1:3), along with 28 patients with UTI as infection controls. The clinical characteristics of patients from the three groups are presented in table 1. Compared with background controls, patients with VZV infections were on average 5 years older. The overall organ involvement, disease duration, SLEDAI at infections or visits, and previous exposure to IS agents were compatible. However, patients who had VZV received slightly but significantly more prednisone (16.45 ± 7.88 vs 11.90 ± 7.50 mg/day, $p = 0.001$) within 3 months prior to the infections. As compared with the infection controls, the baseline clinical parameters were similar between the VZV group and UTI group, including age and prednisone exposure. More importantly, IS agents tend to be suspended or tapered in patients after an infection event, which may contribute to the subsequent lupus flare; thus, UTI controls served as a crucial comparison with VZV in terms of evening out this effect. The rates of flare from the three groups in the index period and control period are shown in figure 2A.

We found that disease flare within the index period was more frequently observed after VZV infections compared with background controls (34.0% vs 9.9%, $p = 0.0003$) or UTI controls (34.0% vs 7.7%, $p = 0.01$). Of the 16 flares in the VZV group during the index period, 10 were major flares, including 6 with new onset or relapse of lupus nephritis, 3 with episode of neuropsychiatric lupus and 1 with mesenteric vasculitis, and 6 were mild or moderate flares manifested as fevers in 3, rashes in 2 and arthritis in 1 patient. Of the 14 flares in the background controls, 7 were major flares, of which 3 with lupus nephritis, 1 with neuropsychiatric lupus, 1 with pleural effusion, 1 complicated with newly onset antiphospholipid syndrome, and 1 with profound alopecia who was treated with tofacitinib. In the UTI group, one major flare manifested as refractory pleuritis and one mild/moderate flare with fever were observed. All patients fulfilled the SFI major flare criteria with more than 0.5 mg/kg/day prednisone prescribed or significant IS agent added on or switched. As comparison, UTI did not seem to increase lupus flares within the index period. When investigating the control period, the VZV infection-related flare rates came down back to a background level as the other two control groups (12.8% vs 8.5% vs 7.1%, $p = 0.40$ and $p = 1.00$).

Kaplan-Meier curve showed that the 3-month flare-free survival of patients with VZV infections was significantly lower than the background controls (66.0% vs 90.1%, $p = 0.0003$), but the non-cumulative difference diminished during the control period. In addition, the UTI controls had a precisely overlapped flare-free curve as with the background controls (figure 2B).

To further confirm the effect of VZV infection on disease flares, we performed proportional hazards regression Cox model. After adjusting for multiple confounders including age, gender, previous organ involvement, baseline disease activity, prednisone, HCQ and IS agents, we

Table 1 Characteristics of three groups: clinical parameters of patients with VZV/UTI and matched background controls at the time of infections or visits

	VZV (n=47)	Background (n=141)	P value (vs VZV)	UTI (n=28)	P value (vs VZV)
Age	40.89±13.79	35.42±13.51	0.018	47.71±14.57	0.046
Gender (female, %)	97.9	90.9	0.14	100	0.44
Disease duration (years)	5.26±4.79	4.99±5.11	0.75	7.56±7.06	0.10
Organ involvement	2.36±0.85	2.28±0.86	0.56	2.46±0.74	0.60
SLEDAI	4.15±1.35	3.69±2.33	0.20	4.03±1.5	0.41
HCQ exposure (%)	89.4	91.5	0.78	92.9	0.71
Prior daily prednisone*	16.45±7.88	11.90±7.50	0.001	15.14±6.13	0.45
Prior IS (%)*	63.8	58.2	0.50	50.0	0.25
CTX	9 (30.0%)	9 (11.0%)	–	3 (17.4%)	–
MMF	10 (33.3%)	30 (36.6%)	–	5 (34.8%)	–
CNI	2 (6.7%)	5 (6.1%)	–	1 (8.7%)	–
AZA	4 (13.3%)	13 (15.9%)	–	2 (17.4%)	–
MTX	4 (13.3%)	19 (23.2%)	–	3 (13.0%)	–
Others	1 (3.3%)	6 (7.3%)	–	0 (0%)	–
Subsequent daily prednisone*	13.62±6.01	10.31±6.51	0.002	12.59±4.98	0.45
Subsequent IS (%)*	48.9	63.9	0.09	42.9	0.64

p values in bold: $p < 0.05$

*Prior daily prednisone and IS: medications used during the baseline period until infections/visits; subsequent daily prednisone and IS: medications used before flares within the index period.

AZA, azathioprine; CNI, calcineurin inhibitors; CTX, cyclophosphamide; HCQ, hydroxychloroquine; IS, immunosuppressive; MMF, mycophenolate mofetil; MTX, methotrexate; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; UTI, bacterial infections of the lower urinary tract; VZV, varicella zoster virus.

confirmed that VZV infection but not UTI was an independent risk factor for disease flare within the index

A

Lupus flares within 6 months after infections or visits.

Flares (0-6m)	VZV (n=47)	Background (n=141)	<i>p</i> (vs background)	UTI (n=28)	<i>p</i> (vs background)
0-3m	16 (34.0%)	14 (9.9%)	0.0003	2 (7.1%)	1.00
Major	10 (62.5%)	7 (50.0%)	/	1 (50.0%)	/
Mild/Moderate	6 (37.5%)	7 (50.0%)	/	1 (50.0%)	/
3-6m	6 (12.8%)	12 (8.5%)	0.40	2 (7.1%)	1.00
Major	2 (33.3%)	5 (50.5%)	/	2 (100%)	/
Mild/Moderate	4 (66.7%)	7 (49.5%)	/	0 (0%)	/

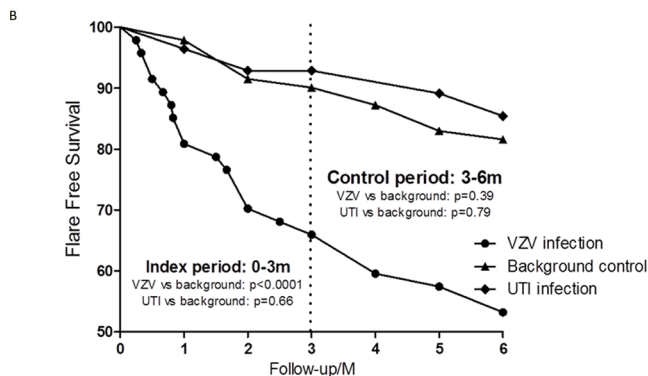


Figure 2 Lupus flares and survival curve. (A) Disease flares within 0–3 months and 3–6 months after VZV/UTI infections or visits. (B) Kaplan-Meier curve of patients from three groups within the index and control period. UTI, bacterial infections of the lower urinary tract; VZV, varicella zoster virus.

period (HR=3.70, 1.67–8.18) (online supplementary table S1).

In order to reduce the effect of baseline clinical characteristics on disease flares in the three groups, especially disease severity and intensity of IS therapy, we applied inverse probability treatment weighting analysis. After adjustment, the characteristics of patients from the three groups at the time of the infections or visits were similar (online supplementary table S2). We reinforced the significant association between recent VZV infections and disease flares (HR 4.16, 1.97–8.77), but UTI did not increase the risk (HR 0.52, 0.10–2.83).

DISCUSSION

Disease flare is a major issue in SLE, with a reported annual rate of 7%–32% according to different definitions.^{9–11} Viral infections have been postulated as contributing factors of lupus flares.^{3 8 12} In the current study, we are aiming to testify whether VZV, a common and well-defined viral infection in SLE, could associate with disease flares.

In our single-centre lupus cohort, the incidence of VZV reactivation was 15.8 per 1000 person-years, which is compatible with previous reports.⁵ First, in order to balance the infection event-related and unrelated effects, we set up two types of controls. One is a 1:3 matched SLE background control group, while the other is the UTI

control group. Second, since the baseline disease activity and intensity of IS therapy before and after the infection event are crucial confounders that contribute to possible subsequent disease flares, we excluded patients with major flares within the baseline period and patients who had been exposed to long-acting biologics (rituximab). Thus, all patients were normalised, to some extent, to a relatively stable background of disease and treatment exposure. Third, we chose the first 3 months after infection as the index period to capture the possible 'cause-effect' flare event; in addition, a control period in the subsequent 3 months was set up as internal control. Finally, to further adjust for confounders such as age, disease duration, previous organ involvement, baseline SLEDAI, prednisone, HCQ and IS agents exposure, we performed Cox regression and propensity score weighting. Our data verified that VZV infection but not UTI was an independent risk factor for disease flare within the index period (HR 3.70–4.16).

The major limitation of the current study is its retrospective design and limited number of VZV and controls. A prospective study with a larger sample size needs to be carried out. Particularly, since new VZV vaccine is on the horizon, a multicentre, prospective clinical trial with an endpoint to assess whether the vaccination could reduce lupus flares would be of high interest.

Contributors All authors participated in drafting and revising the article, and all authors approved the final version for publication. SY had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data. Study design: SY. Acquisition of data: FS, YC, WW, LiG. Analysis and interpretation of data: FS, YC.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The retrospective study protocol was approved by the ethics committees of Ren Ji Hospital.

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