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Cervical neoplasia in systemic lupus erythematosus: a nationwide study

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Abstract

Objective. The aim was to examine the risk of cervical neoplasia in women with SLE, overall and with respect to treatment, compared with women from the general population.

Methods. By linking national Swedish registers, we assembled a cohort including women with SLE (n = 4976) and matched general population comparators (n = 29 703). Two subcohorts of treated SLE patients were defined on the basis of treatment with antimalarials (n = 1942) and other immunosuppressants (AZA, CYC, ciclosporin, MTX, MMF or rituximab; n = 2175). The main outcome was defined as a first cervical neoplasia (dysplasia or cancer) during follow-up. Secondary outcomes were first cervical intraepithelial neoplasia (CIN) 1; first CIN grades 2–3; and first invasive cervical cancer during follow-up (2006–12). Cox regression models estimated relative risks adjusted for age, level of education, healthcare utilization, number of children, marital status, family history of cervical cancer and prior cervical screening.

Results. Based on 121 events of cervical neoplasia during 23 136 person-years among SLE patients, there was an increased risk of any cervical neoplasia compared with the general population [hazard ratio (HR) = 2.12 (95% CI: 1.65, 2.71)]. The risk of CIN 1 [HR = 2.33 (95% CI: 1.58, 3.44)], CIN 2–3 [HR = 1.95 (95% CI: 1.43, 2.65)], but not invasive cervical cancer [HR = 1.64 (95% CI: 0.54, 5.02)], was increased in women with SLE. The subcohort treated with other immunosuppressants was at highest risk of cervical neoplasia.

Conclusion. SLE is a risk factor for cervical neoplasia, in particular for pre-malignant cervical lesions. Among patients with SLE, the risk is higher among those treated with immunosuppresants compared with those treated with antimalarials.

Key words: systemic lupus erythematosus, cervical cancer, immunosuppressants, antimalarials, cohort study, registers, epidemiology, reproductive, DMARDS, viruses.

Rheumatology key messages

- Women with SLE appear to be at increased risk of cervical neoplasia.
- Treatment with systemic immunosupressants is a marker of higher risk among women with SLE.

Introduction

SLE demonstrates a marked female predominance, is associated with numerous immunological aberrations involving both innate and adaptive immunity [1], and is typically treated with various immunomodulatory regimens. Immunosuppressive agents such as AZA, CYC and ciclosporin are known carcinogens and used in SLE [2]. Several studies have suggested that an increased risk of cervical neoplasia in SLE is, at least in part, attributable to the immunosuppressive treatment [3, 4].

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Previous studies have suggested a small increase in the overall burden of cancer in SLE [5–7], but the risks for cervical pre-malignancies and invasive cancer are less well understood. Studies to date have suggested suboptimal use of screening in women with SLE and an increased risk of cervical dysplasia [8, 9], but whether there is an increased risk for invasive cervical cancer remains unclear [5, 10].

In light of the immunological aberrations associated with SLE, the immunomodulatory drugs used to treat it, and the fact that the risk of cervical neoplasia can be effectively reduced by HPV vaccination and cervical cancer screening [11, 12], a better understanding of these risks is of direct clinical relevance. The aim of this study was therefore to assess the incidence of pre-malignant and invasive cervical malignancies in women with SLE, and to compare these risks with those in the general population. Women with SLE were considered overall and as defined by treatment exposures.

Methods

Study design

We performed a nationwide cohort study with follow-up from January 2006 to December 2012, using population-based data from Swedish national registers on patients with SLE, cervical cancer screening and invasive cervical cancer.

Setting and data sources

Swedish health care is public and tax funded. All Swedish residents are assigned a personal identification number, which allows for linkage between registers. This study was based on the Swedish Lupus Linkage cohort, which has been described in detail elsewhere [13]. Briefly, the National Patient Register (NPR) contains data on hospitalizations since 1969 and outpatients visits in specialized care since 2001, and lists main and contributory diagnoses, dates of admission and discharge, hospital and department. Diagnoses are assigned by the discharging/treating physician and coded according to international classification of disease (ICD) codes versions 7–10. The Prescribed Drug Register (PDR) lists all dispensings of prescription drugs from pharmacies in Sweden since July 2005. The Swedish Cancer Register began in 1958 and captures the mandatory reporting of incident cancers along with date, diagnosis, site of tumour, tumour stage and tumour histology. Cervical cancer is staged according to the International Federation of Gynecology and Obstetrics classification system. During the study period, all women living in Sweden were invited to cervical screening every 3 years between ages 23 and 50 years, and every 5 years between ages 51 and 60 years. The Swedish National Cervical Screening Registry (NKCx) gathers data on all Papanicolaou smears and ensuing histology or cytology analyses. The Cause of Death Register records the date and underlying and contributory causes of death. The Total Population Register contains information on residency and dates of immigration or emigration for all residents in Sweden since 1961. The Multigeneration Register contains information on parents and children of those born in Sweden in 1932 or later and those registered in Sweden at some time since 1961. Siblings can be identified by listing all persons with the same biological parents.

Study population

The full SLE cohort was defined as all women who had at least two discharge diagnoses with an ICD code specifying SLE from the Patient Register (ICD-8 734.1, ICD-9 710.0 and ICD-10 M32) including at least one outpatient visit at a department or specialist typically known to diagnose, treat or manage SLE (rheumatology, dermatology, nephrology, internal medicine and paediatrics), between 1 January 2001 and 31 December 2012. The date of the second SLE-coded visit served as the start of follow-up. Drug-induced lupus (ICD-10 M32.0) was not included. Within the full SLE cohort, we identified two nested and overlapping subcohorts based on medication dispensing.

The first subcohort consisted of patients treated with antimalarials who had at least one dispensing of HCQ or chloroquine phosphate. The start of follow-up was defined as the date when all inclusion criteria were fulfilled (i.e. medication and the SLE-coded visits described above, January 2006 or later). Any dispensing for immunosuppressant medications listed below resulted in exclusion if prior to the start of follow-up, and censoring (and subsequent switching of subcohorts) if following the start of antimalarial therapy.

The second subcohort consisted of SLE patients treated with immunosuppressants who had at least one dispensing of MMF, AZA, CYC, ciclosporin, MTX or rituximab in the PDR. The start of follow-up was defined as the date when all of the SLE diagnoses and date of first immunosuppressant dispensing criteria were fulfilled. Person-time in this subcohort was classified as once exposed, always exposed.

Through Statistics Sweden, comparator subjects from the general population were identified and matched to each individual with SLE (5:1), on sex, year of birth and county of residence. Matching was not preserved after applying further exclusion criteria, but matching factors were accounted for in the analyses. The start of follow-up was set as the same date as their respective index individual with SLE.

Women who had undergone a total hysterectomy or had solid organ transplantation prior to or during follow-up were excluded or censored, respectively. Women with a history of invasive cervical cancer were also excluded. Women could not contribute person-time to the study until they turned 23 years old, at which point they were eligible for the national screening programme. Ethical approval was obtained by the Ethical Review Board of Karolinska Institutet.

Outcomes

Using the NKCx and Cancer Register, the main outcome was a composite outcome defined as follows:

a first ever histopathological diagnosis of cervical intraepithelial neoplasia (CIN) 1 (including atypical glandular cells), CIN 2^+, which was defined as CIN 2–3 (including adenocarcinoma *in situ*), or invasive cervical cancer. CIN 1–2 were identified from NKCx. CIN 3 was identified from both NKCx and the Cancer Register, and invasive cervical cancer was identified from the Cancer Register.

The composite primary outcome was split into three secondary outcomes and analysed separately. The first secondary outcome was a first ever histopathological diagnosis of CIN 1, in women with no history of cervical dysplasia. The second secondary outcome was a first ever histopathological diagnosis of CIN 2^+. The third secondary outcome was a first ever diagnosis of invasive cervical cancer.

Additional covariates

We identified and defined a number of potential confounders, including educational level (three categories: $\leqslant$9, 10–12 and $>$12 years), family history of cervical cancer in a first degree relative (yes/no), and cervical screening within 5 years prior to the start of follow-up (yes/no). The combined number of non-primary care outpatient visits and hospitalizations in the NPR during the last 2 years before the start of follow-up was a marker of the intensity of health-care contacts and frailty and dichotomized using the general population comparator's 75th percentile as a cut point (frequent = 3 or more/non-frequent utilizer = 2 or less). Number of biological children identified in the multigeneration register served as a marker of parity (three categories: 0, 1–2, 3 or more). Use of oral steroids at the start of follow-up was determined by recorded use in the PDR within 3 months before the start of follow-up, and use of oral contraceptives (OCs) by recorded use within 6 months before the start of follow-up.

Statistical analysis

We assessed the total number of events, person-years at risk and estimated incidence rates of each outcome in each cohort. The end of follow-up was defined as the first of 31 December 2012, the outcome under study, death, emigration, total hysterectomy or solid organ transplant. We compared participation in cervical screening by exposure and age groups, the latter to account for different screening recommendations. Among screening participants, we estimated the mean time to first cervical screening during follow-up and the corresponding variance for each age-exposure group and compared the groups using *t*-tests. The time to first observed cervical screening was used as a proxy for the average rate of screening. For all outcomes, we compared the full SLE cohort with the general population, and the two treatment-defined subcohorts with one another. We used Cox regression, with age as the time scale, to estimate hazard ratios (HRs) and their corresponding 95% CIs, adjusting for the covariates specified above, including health-care utilization, education, number of children, marital status, previous screening and family history of cervical cancer. In analyses comparing the two SLE subcohorts with each other, we also adjusted for use of oral steroids within 3 months and OC within 6 months prior to the start of follow-up. All covariates were treated as time fixed and reflective of status at the start of follow-up. To investigate effect modification by age and thus any non-proportionality over the time scale used, we plotted hazard functions, introduced an interaction term between the exposure and the time scale, and stratified analyses on three age bands (23–44, 45–64 and 65^+ years old). Cells with fewer than five events were not presented because of identifiability issues.

Sensitivity analyses

We examined risks among women who were diagnosed with SLE for the first time in the NPR $<$2 years prior to the start of follow-up. Also, we analysed models adjusted for use of oral steroids during follow-up in a sensitivity analysis. Lastly, in another sensitivity analysis, patients with at least one dispensing of LEF, tacrolimus or sirolimus were also included in the immunosuppressants subcohort.

Results

Baseline characteristics

The full SLE cohort consisted of 4976 women with SLE, of whom 1942 fulfilled the entry criteria for the antimalarials subcohort, and 2175 for the immunosuppressants subcohort; 473 individuals were in both subcohorts. On average, patients in the treated subcohorts were younger than those in the full SLE cohort. The antimalarials subcohort had shorter estimated disease duration at the start of follow-up (median 2.5 years since first outpatient visit) compared with the immunosuppressants subcohort (3.7 years). Patients in the immunosuppressants subcohort were more likely to have co-morbidities and be on oral steroids at baseline than those in the antimalarials group (Table 1). Total use of OCs was similar between the cohorts, but women with SLE were more often dispensed OC without oestrogen than the general population.

The proportion of SLE patients (full cohort) who were screened at least once during follow-up (55%) was similar to the corresponding proportion in the general population comparator cohort (58%). In the treatment-defined SLE subcohorts, these proportions were 46% in the antimalarial and 56% in the immunosuppressants subcohort, and their mean follow-up times were shorter than the full SLE-cohort (3.7 and 4.6 *vs* 5.2 years, respectively). Cox regression analyses of time to first screen, taking age and follow-up time into account, revealed no differences across any of the SLE cohorts and *vs* the general population (supplementary Table S1, available at *Rheumatology* Online).

Occurrence and relative risk of cervical neoplasia in SLE *vs* general population

During $\sim$24 000 person-years in the full SLE cohort, there were 53 cases of CIN 1, 75 cases of CIN 2^+ and 5 cases of invasive cervical cancer (Table 2). SLE was associated with a $>$2-fold increase in the rate of cervical neoplasia [dysplasia or invasive cancer; HR = 2.12 (95% CI: 1.65, 2.71)]. When considered separately, the rates of CIN 1

Table 1 Characteristics of the study population of Swedish women with SLE and matched subjects

Characteristics at start of follow-up	Full SLE	General population	P-value[b]	Anti-malarials[a]	Immunosuppressants[a]	P-value[c]
n	4976	29 703		1942	2175	
Age at entry, median (IQR), years	51 (38–63)	51 (38–63)	0.40	49 (37–61)	46 (35–59)	<0.001
Time since first SLE diagnosis in the outpatient register[d], median, years	3.2			2.5	3.7	<0.001
Time since first SLE diagnosis in the patient register[e], median, years	3.9			3.1	4.4	<0.001
Educational level, %						
⩽9 years	24	21		21	21	
9–12 years	43	43		45	44	
>12 years	33	35	<0.001	34	35	0.81
Oral steroids[f], %	38			35	57	<0.001
Oral contraceptives containing oestrogen[f], %	3.4	6.8	<0.001	4.0	3.0	0.10
Oral contraceptives without oestrogen[f], %	7.6	5.6	<0.001	9.5	9.3	0.84
Number of outpatient visits and hospitalizations during last 2 years preceding start of follow-up, mean	10.3	2.2	<0.001	8.8	13.8	<0.001
Co-morbidities, ever prior to start of follow-up, %						
Chronic obstructive pulmonary disease	3.4	1.3	<0.001	2.5	3.5	0.06
Diabetes mellitus	4.3	2.8	<0.001	2.7	5.1	<0.001
Ischaemic heart disease	8.7	3.2	<0.001	5.7	8.3	0.001
Cervical screening characteristics						
Number of cervical screens during last 5 years preceding start of follow-up, mean (range)	1.17 (0–12)	1.09 (0–15)	0.07	1.25 (0–10)	1.25 (0–12)	0.86
Time since last cervical screening visit at date of start of follow-up, median, years	2.8	2.9	0.03	2.5	2.6	0.13
History of CIN 1 within 5 years before start of follow-up, %	0.9	0.4	<0.001	0.9	1.4	0.18
History of CIN 2^+ within 5 years before start of follow-up, %	1.0	0.8	0.09	1.1	1.2	0.63

[a]Subsets of full SLE. [b]Full SLE *vs* general population. [c]Antimalarials *vs* immunosuppressants. [d]Outpatient register available since 2001. [e]Outpatient since 2001 or inpatient visits nationwide since 1987. [f]Data on exposure from the Prescribed Drug Register 2006. CIN: cervical intraepithelial neoplasia; IQR: interquartile range.

and CIN 2^+ were significantly increased [HR = 2.33 (95% CI: 1.58, 3.44) and HR = 1.95 (1.43, 2.65), respectively], but not the rates of invasive cervical cancer [HR = 1.64 (95% CI: 0.54, 5.02)] (Table 2).

Occurrence and relative risk of cervical neoplasia in subsets of patients with SLE as defined by treatment

In head-to-head comparisons, immunosuppressant therapy was associated with an ~1.8-fold higher risk for the composite primary outcome [HR = 1.83 (95% CI: 1.15, 2.91)] compared with antimalarial treatment. Furthermore, the immunosuppressants subcohort had an increased rate of CIN 1 [HR = 2.33 (95% CI: 1.08, 5.02)], but not of CIN 2^+ [HR = 1.44 (95% CI: 0.82, 2.54); Table 2]. All five cases of invasive cervical cancer were in the immunosuppresants subcohort, thus Cox regressions were not performed.

Stratified and sensitivity analyses

Stratifying the analyses in different age bands did not reveal any obvious heterogeneity in risks across these age groups (Table 3). Sensitivity analyses restricted to patients with SLE first presenting in the registers no more than 2 years prior to earliest start of follow-up did not markedly alter the results (supplementary Table S2, available at *Rheumatology* Online). The results of models that were additionally adjusted for oral steroids during follow-up did not differ from the fully adjusted models (supplementary Table S3, available at *Rheumatology* Online). The sensitivity analysis that included patients with dispensings of LEF, tacrolimus or sirolimus in the immunosuppressants subcohort added only five patients in the immunosuppressants subcohort, and yielded similar results to the main analysis (data not shown).

Table 2 Risk of cervical dysplasia and invasive cervical cancer among SLE patients and matched subjects

Outcome definition	Number of patients at risk	Number of events	Total follow-up, years	Crude incidence per 100 000 person-years	Fully adjusted HR (95% CI)[b]
Composite outcome of cervical dysplasia and cancer					
Full SLE	4550	121	23 136	523	2.12 (1.65, 2.71)
General population	28 113	336	155 543	216	Reference
Immunosuppressants[a]	1981	73	9002	811	1.83 (1.15, 2.91)
Antimalarials[a]	1783	26	6564	396	Reference
First ever CIN 1					
Full SLE	4550	53	23 136	229	2.33 (1.58, 3.44)
General population	28 113	115	155 543	74	Reference
Immunosuppressants[a]	1981	30	9002	333	2.33 (1.08, 5.02)
Antimalarials[a]	1783	9	6564	137	Reference
First ever CIN 2^+					
Full SLE	4619	75	23 589	318	1.95 (1.43, 2.65)
General population	28 299	232	156 738	148	Reference
Immunosuppressants[a]	2022	43	9229	466	1.44 (0.82, 2.54)
Antimalarials[a]	1812	19	6687	284	Reference
First ever invasive cervical cancer					
Full SLE	4976	5	25 666	19	1.64 (0.54, 5.02)
General population	29 703	17	165 412	10	Reference
Immunosuppressants[a]	2175	5	10 011	50	NA[c]
Antimalarials[a]	1942	0	7268	0	Reference

[a]Subsets of Full SLE. Data on exposure from the Prescribed Drug Register 2006 to date. [b]Adjusted for level of education, health-care utilization, number of children, marital status, family history of cervical cancer, prior cervical screening and start year. Models comparing SLE immunosuppressants *vs* SLE antimalarials were additionally adjusted for use of oral contraceptives and oral steroids at baseline. [c]HRs were not calculated if there were fewer than five events in the smallest cell. CIN: cervical intraepithelial neoplasia; HR: hazard ratio.

Table 3 Risk of cervical dysplasia stratified on attained age, SLE *vs* general population

Outcome definition	Age, years	Age-adjusted HR (95% CI)
Composite outcome of cervical dysplasia and cancer	18–44	2.30 (1.81, 2.93)
	45–64	2.76 (1.81, 4.20)
	⩾65	NA[a]
First ever CIN 1	18–44	2.69 (1.80, 4.02)
	45–64	3.80 (2.16, 6.68)
	⩾65	NA[a]
First ever CIN 2^+	18–44	2.09 (1.57, 2.79)
	45–64	1.96 (1.06, 3.65)
	⩾65	NA[a]

[a]Hazard ratios were not calculated if there were fewer than five events in the smallest cell. CIN: cervical intraepithelial neoplasia; HR: hazard ratio; NA: not assessed.

Discussion

The main findings of this study were that compared with the general population, women with SLE have higher rates of cervical neoplasia. Women with SLE treated with immunosuppressant therapies such as MTX, AZA and MMF appeared to be at highest risk.

With five cases of invasive cervical cancer among almost 5000 women with SLE, our study is one of the largest to date. Our finding of an increased risk of cervical dysplasia in women with SLE is in line with most recently published studies on cervical dysplasia or composite outcomes of high-grade dysplasia and cervical cancer [8, 9]. We did not find an association between SLE overall and invasive cervical cancer, although the point estimate of relative risk was >1. All five invasive SLE cases were among the immunosuppressant-treated group, suggesting that there may be features related to the treatment, its indication or other features that might explain the association. Several of the largest studies to date have also found non-significant increased risks [5, 14]. A Danish cohort study that included 576 SLE patients reported an increased risk of both invasive HPV-associated malignancies and dysplasia or carcinoma *in situ* of the cervix in SLE patients compared with general population standardized incidence ratios [15]. A large study conducted on the California Cancer Registry reported a significantly lower risk of cervical cancer among women with SLE compared with the general population [16]. Their study reported high rates in the general population and ended follow-up time in 2002; these factors and other methodological differences in case and outcome definitions may explain the different findings. The same study reported an increased risk of cancer of the vagina/vulva, which is also an HPV-associated cancer.

Although we found consistently higher rates of cervical neoplasia among patients with SLE treated with immunosuppressants compared with those who were treated only with antimalarials, small numbers hampered such comparisons for the outcomes CIN 2^+ and invasive cervical cancer.

Some studies have found that increased risk of cervical dysplasia in women with SLE might be attributable to immunosuppressant treatments [4, 17, 18]. A large register-based study from Denmark found a dose-dependent increased risk of cervical cancer among patients with autoimmune diseases treated with AZA [19]. However, a large study by Kim *et al.* [8] examined the risk of high-grade cervical dysplasia or cervical cancer from two commercial US health plans. Using female patients without systemic inflammatory diseases as the reference, the HR for SLE patients treated with systemic immunosuppressants was similar to that of SLE patients not treated with systemic immunosuppresants [8].

Women with SLE are recommended to avoid OC containing oestrogen because it might worsen disease activity. This might make OC an inappropriate proxy for sexual activity in comparisons between women with SLE and the general population. Therefore, we adjusted for OC only in analyses comparing patients treated with antimalarials with those treated with immunosuppressants, which might still result in some residual confounding. HPV vaccination was introduced during the study period, but because most women in this study were middle-aged, vaccination penetrance is likely to have been very low [12].

Regarding screening, we noted some numerical differences in the proportion of women who underwent at least one screen during our follow-up. These differences might be attributable to differential lengths of follow-up time in the cohorts and were not reflected in the Cox regression investigating time to first screen. However, we cannot rule out the possibility that some differences in screening behaviour might explain some of our findings. Two previous studies assessed cervical screening among women with SLE. A study from Denmark presented similar 4-year cervical screening participation proportions among women with SLE and the general population [19], whereas a study among Canadian women with SLE found lower self-reported participation in cervical screening in the previous 12 months compared with community rates [20]. In our study using a cervical cancer screening register, the proportion of younger women attending a screening visit was lower in the two treatment-defined SLE subcohorts, which may have been because of a shorter duration of follow-up in these groups. Our data suggest that these difference are, however, relatively small.

There are some limitations that should be mentioned. First of all, we did not have data on drug dispensings prior to July 2005, when the PDR was started; therefore, medication exposure and history among prevalent SLE cases may have been misclassified. However, restriction to patients with more recent SLE presentation did not yield markedly different results. Additional treatment misclassification may exist because the PDR typically includes only medications dispensed at a pharmacy; therefore, medications administered primarily or solely as infusions or during the clinical visit, such as rituximab and CYC, are likely to be missed (although most such patients also have treatment exposures such that they would qualify for the immunosuppressants subcohort). The observed differences in the risk of cervical neoplasia between the SLE subcohorts might be attributed to disease severity rather than to drug exposure. Although some aetiological uncertainty therefore remains, the clinical implication is still that patients treated with immunosuppressants are at increased risk and should be adequately monitored, regardless of whether the risk increase is attributable to disease severity or treatment. We could not adjust for smoking, which might increase the risk of both cervical neoplasia and SLE [21]. However, if we assume extreme values for the prevalence of smoking among women with lupus greater than those reported in the literature [22], smoking would account for only part of the increased risk (supplementary Table S4, available at *Rheumatology* Online). Unfortunately, we did not have data on HPV infection, which is a known risk factor for cervical cancer. Despite the population-based nationwide data and relatively large cohort, the power to detect significant differences in invasive cervical cancer risk was still limited. In the secondary outcomes, competing risks of earlier phases of the disease may introduce some bias. Our comparisons neither censored nor excluded individuals with dysplasias when evaluating invasive cervical cancer as the outcome. This would be likely to yield a conservative estimate of the relative risk because these individuals continued to contribute person-time after they had experienced an event that could lower their risk of the outcome through intensified screening, surgical intervention or other treatment. As the composite end point considered all outcomes as along the same aetiological trajectory, this primary outcome measure was not subject to bias attributable to competing risks.

The use of prospectively collected, nationwide register data, which avoids the risk of recall bias and increases the generalizability, was a major strength to this study. Results should be generalizable to countries with a similar health-care setting with readily available cervical screening and universal health-care coverage with very low out-of-pocket costs. Linking our cohorts to other databases allowed us to account for important potential confounders and other factors, such as educational level, prior cervical screening, drug exposures, family history of cervical cancer and parity. Histopathology data allowed us to study a chain of outcomes, from CIN 1 to invasive cervical cancer, which is something few other studies have been able to do.

In conclusion, this study suggests that women with SLE are at increased risk of cervical neoplasia, in particular pre-malignant lesions. The risk is higher among SLE patients treated with immunosuppressants compared with those treated with antimalarials. Treating physicians should be aware of the importance of preventative measures, such as cervical screening and HPV vaccination,

especially for SLE patients treated with potent immunosuppressants.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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