

Increased prevalence of Lupus Co-morbidity in Patients with Psoriatic Arthritis: A Population-Based Case-Controlled Study

Danielle Korkus¹, Tal Gazitt^{2*}, Arnon Dov Cohen^{3,4*}, Ilan Feldhamer³, Idit Lavi⁵, Amir Haddad², Sari Greenberg-Dotan³, Erez Batat³, Devy Zisman^{1, 5}

¹ The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel

²Rheumatology Unit, Carmel Medical Center, Haifa, Israel

³Chief Physician's Office, Central Headquarters, Clalit Health Services, Tel Aviv, Israel

⁴Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheba, Israel

⁵Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel

*Both authors contributed equally to the manuscript

Addresses for correspondence:

Dr. Devy Zisman

Rheumatology Unit

Carmel Medical Center

7 Michal Street

Haifa 34362 Israel

Tel: 972-4-825-0486

Fax: 972-4-826-0013

Email: devyzisman@gmail.com

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Objective: To assess the prevalence of lupus (SLE) in a psoriatic arthritis (PsA) cohort and to compare it to the general population using the database of a large health care provider.

Methods: We analyzed the database of the PsA cohort (2002-2017) matched for age and sex with randomly selected controls for demographics, clinical and laboratory manifestations and dispensed medications. Statistical analysis used student's t-test, Chi square test, as appropriate. In the PsA group, incidence density sampling was performed matching PsA patients without SLE as controls to each case of PsA with SLE by age and follow-up time. Univariable and multivariable conditional logistic regression analysis were used to assess factors affecting SLE development.

Results: The PsA and control groups consisted of 4836 and 24180 subjects, respectively, median age of 56 ± 15 years, 53.8% of whom were female. Eighteen patients (0.37%) in the PsA group and 36 patients (0.15%) in the control group were diagnosed with SLE ($p=0.001$). SLE patients without PsA had higher anti-dsDNA and anti-cardiolipin antibodies. Usage of drugs with known potential to induce SLE was higher in the PsA than in the control group. Older age at PsA diagnosis, shorter PsA duration and statin treatment were associated with SLE in PsA patients.

Conclusion: A 2.3fold increase in the prevalence of SLE in PsA relative to control group was found. Risk factors for SLE development included older age at PsA diagnosis, shorter PsA duration, and statin treatment. The association between PsA and SLE may affect treatment choices and medication development.

Introduction

Psoriatic arthritis (PsA) is an inflammatory musculoskeletal disease with immune-mediated features. The disease is classified as part of the spondyloarthritides. PsA occurs in 25% of individuals with psoriasis, and up to 1% of the general population(1, 2). Patients with psoriasis and PsA can develop a variety of comorbidities including diabetes, hypertension, cardiovascular diseases and depression. PsA patients are more affected than those with isolated psoriasis, and disease severity also increases the prevalence of comorbidities(3). Comorbidities, in turn, may influence the therapeutic regimen and affect treatment outcomes.

Systemic lupus erythematosus (SLE) is an autoimmune disease most common in women of childbearing age. In the United States, the prevalence varies between 20 to 50 per 100,000 women. The disease affects many different organs and the clinical manifestations include musculoskeletal, cutaneous, renal, central nervous system, hematologic, cardiac, and gastrointestinal systems(1). The presence of anti-nuclear antibodies (ANA) is one of the hallmarks of SLE(4). Several studies report higher prevalence of -ANA positivity in patients with psoriasis and PsA(5-7). Previous studies also report a coexistence of psoriasis and SLE(8, 9), but unlike psoriasis, the coexistence of PsA and SLE has only been reported in several case reports(9, 10). Our study objectives were to assess the prevalence of SLE in a PsA patient cohort and to compare it to the general population.

Methods

Study population: The subjects and information used in this study derive from the Clalit health services (CHS) database. The CHS serves approximately 52% of the Israeli population (4.3 million people). The CHS database includes information updated continuously from pharmaceutical, medical and administrative operating systems. Disease codes are registered according to the International Classification of Diseases Ninth Revision (ICD-9) and

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medications dispensed are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The database includes information on all medications dispensed including the date, dose and mode of administration. The database was designed for purposes of administrative and clinical management and is available for use in epidemiological studies. The PsA patient cohort was validated and described in detail in previous studies(11, 12) . For each patient with PsA found in the registry from January 1, 2002 to December 31, 2017, five age- and sex-matched subjects who had no history of psoriasis, PsA, rheumatoid arthritis, or ankylosing spondylitis were chosen as a control group from the entire Clalit database. In both groups, patients with a code diagnosis of SLE were identified. The diagnosis of SLE was then validated based on clinical and laboratory manifestations of the disease using the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (4) by manually exploring the database including rheumatologists and other specialists' clinic visit notes and reviewing hospital discharge summaries and laboratory results.

Demographic data included in this study from the CHS database included age, sex, ethnicity (Jewish/Arab), and socioeconomic status (SES) at enrolment, the latter defined as low, medium, or high categories which correlate highly with the Israel Central Bureau of Statistics categories of SES status and data on body mass index (BMI). In addition, dispensed medications such as glucocorticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), conventional disease modifying agents (cDMARDs), biologic DMARDs (bDMARDs), mycophenolate mofetil, cyclophosphamide, and medications with known potential to induce SLE(13, 14) as well as phototherapy (broad band UVA/UVB, narrow band UVB and PUVA) were analyzed.

In this study, ANA was measured by immunofluorescence (IF) read manually by a laboratory technician and by multiplex bead assay. The cutoff dilution was set on 1:160. Anti-double

stranded DNA (anti-dsDNA) positivity was validated by Crithidia assay (AESKUSLIDES®nDNA Crithidia Lucilia Test, Wendelsheim, Germany).

The study was approved by the Institutional Review Board of Carmel Medical Center (CMC-0014-14). Requirement for individual patient consent forms was waived due to the retrospective, observational nature of the study.

Statistical analysis:

Descriptive analysis of the study population comparing PsA patients with and without co-existing SLE and between this PsA patient group to the control group was performed using Chi-square test and student's t-test, as appropriate. The standardized incidence ratio (SIR) comparing the prevalence of SLE among patients with PsA compared to the control group was calculated, adjusted for age and sex. Post-hoc analysis was used to develop a predictive model for SLE development among PsA patients by using incidence density sampling (SAS/ACCESS version 9.4, released 2013, SAS Institute Inc., Cary, NC) in which we attempted to match 10 comparator PsA female patients without co-existing SLE as controls to each case of PsA with co-existing SLE by date of birth and follow-up time which was defined as date of SLE diagnosis. The association between SLE occurrence, adjusted to PsA duration or age at PsA diagnosis, was analyzed using two separate multivariable conditional logistic regression models: model I which included psoriatic arthritis duration, and model II which included age at PsA diagnosis. A third model, model III, in which we included the entire study population (i.e. the control group and the PsA patient group) analyzing the association of age, sex, PsA diagnosis, ethnicity, and possible culprit medications used prior to SLE diagnosis was used to calculate the risk of SLE development. Odds ratios and 95% confidence intervals were calculated in order to estimate the association between the variables and SLE events. All data was analyzed using SPSS, version 24 (IBM SPSS Statistics

for Windows, version 24.0, 2016, Armonk, NY). All tests were 2-sided; p values of <0.05 were considered statistically significant.

Results

The PsA study group consisted of 4836 subjects, at a median age of 56 ± 15 years, 2603 (53.8%) of whom were females. The control group consisted of 24,180 subjects matched for age and sex. In comparison to the control group, the PsA study group had a lower socioeconomic status (32.2% vs 40.6% $p < 0.0001$), higher percentage of smokers (42.5% vs. 38.3% $p < 0.0001$), higher BMI (28.65 ± 5.8 vs 27.5 ± 5.4 $p < 0.0001$), and had a higher percentage of Jewish patients (87.3% vs 81.5% $p < 0.0001$) relative to Arab patients. Comparing comorbidities between the study and control groups shows that the study group had a statistically significant higher incidence of hyperlipidemia (64.6% vs 56%, $p < 0.0001$), hypertension (42.1% vs 34.7%, $p < 0.0001$), diabetes mellitus (28% vs 22.1%, $p < 0.0001$), malignancy (20.3% vs 11.2%, $p < 0.0001$), osteoporosis (12.9% vs 9.8%, $p < 0.0001$), obesity (38.3% vs 28.1%, $p < 0.0001$), congestive heart failure (4.5% vs 3.2%, $p < 0.0001$), ischemic heart disease (15.8% vs 12.4%, $p < 0.0001$) and cerebrovascular accident (6.3% vs 5.4%, $p < 0.0001$) [Table 1].

Overall, out of this PsA cohort, 18 patients (0.37%) met SLE classification criteria vs 36 patients (0.15%) in the control group, $p = 0.001$ [Table 1]. The calculated SIR comparing the prevalence of SLE among patients with PsA to the control group reached 2.36 adjusted for age and 2.81 after adjusting for age and sex. Ten patients were diagnosed with SLE before PsA diagnosis with a mean of 15.62 ± 17.48 years and a median of 10.46 years. Eight patients were diagnosed with PsA before SLE diagnosis with a mean of 4.84 ± 6.79 years and a median of 2.45 years.

SLE patients without co-existing PsA were more positive for anti-dsDNA (92.3% vs 66.7%, $p = 0.022$) and anti-cardiolipin (ACL) antibodies (47.2% vs 16.7%, $p = 0.038$). Anti –histone

antibodies were found in 6/36 (16.7%) in controls and in the same percentage of PsA patients 3/18 (16.7%). No other significant differences were observed between the two groups in terms of clinical and laboratory manifestations of SLE [Table 2]. PsA patients with concomitant SLE versus PsA patients without SLE were more often female (100% vs 53.7%, $p<0.0001$), had more osteoporosis (38.9% vs 12.8%, $p=0.005$) and were more likely to be treated with beta blockers (27.8% vs 9.8% $p=0.027$) [Table 3]. Usage of medications with known potential to induce SLE prior to diagnosis of SLE was higher in the study group of PsA patients with concomitant SLE (11 out of 18 patients) than in the control group. Possible culprit medications associated with later onset of SLE included proton pump inhibitors (PPI) 0.27% in the PsA cohort vs 0.1% in the control group ($p=0.004$), beta blockers 0.33% vs 0.16% ($p=0.011$), angiotensin converting enzyme inhibitors (ACE-I) 0.35% vs 0.13% ($p=0.001$), thiazide diuretics 0.35% vs 0.1% ($p=0.001$), and anti-tumor necrosis factor (anti-TNF) agents 0.4% vs 0.2% ($p=0.002$). [Table 1] None of the 18 patients in the PsA group were treated with phototherapy prior to SLE diagnosis. No difference in clinical manifestations of SLE were observed between patients treated with medications known to induce SLE relative to SLE patients not on such medications [Table 3]. Out of the PsA group of 4,836 patients, 4,062 were examined for ANA positivity, with 1,189 (29.3%) having a positive test result at some time point over their follow-up period.

Using two different multivariable conditional logistic regression models, we analyzed potential risk factors for future development of SLE among PsA patients by matching 131 patients with PsA to the 18 PsA patients who developed SLE [Table 4]. In model I, where psoriatic arthritis duration was analyzed, we found an inverse relationship between PsA duration and SLE development so that patients with long-standing PsA were at lower risk of SLE development (OR 0.82, CI 0.69-0.98, $p=0.03$); in model II, where age at PsA diagnosis was analyzed, we found a direct relationship between age at PsA onset and risk of developing SLE, so that patients with later onset of PsA were at higher risk of SLE development relative

to patients with early-age onset of PsA (OR 1.25, CI 1.06-1.48, $p=0.008$). Statin therapy was also found to increase the risk of SLE onset among PsA patients [Table I, $p<0.0001$]. In model III in which we included the entire study population consisting of the control and the PsA patient groups with SLE development as outcome (table 5), we found that female sex and PsA diagnosis were risk factors for SLE development. In this model, statin use was no longer a statistically significant risk factor for SLE development.

Discussion

In our study, which is the first retrospective, large population study to report on the co-existence of PsA and SLE, we found a 2.3-fold increase in the prevalence of SLE among PsA patients compared to age and sex-matched controls out of the general population (0.37% vs 0.15% $p=0.001$ and calculated SIR equal to 2.81). We did not find significant differences in comparing SLE disease manifestations between these two groups. We observed that 24.6% of PsA patients tested positive for ANA. This percentage is lower than the prevalence published in previous literature. For instance, Johnson et al. found that 47% of PsA patients had ANA positivity at a 1:40 dilution(5), while Silvy et al. found 57% ANA positivity at a 1:100 dilution and 52% ANA positivity at a 1:160 dilution cutoffs(7) among PsA patients where ANA testing was done as a two-step assay with immunofluorescence (IF) read by a laboratory technician followed by a separate multiplex bead assay. Therefore, differences in study populations and laboratory testing techniques might account for these differences.

In our study cohort, SLE was more prevalent among women with co-existing PsA than in men (100% vs. 53.7%, $p<0.0001$). Current literature shows no difference in occurrence of PsA among males and females in the general population. For instance, a study by Ritchlin et al. demonstrated a 1:1 male to female ratio in this regard(15), as does a study by Mease et al.(16) Conversely, a few other studies showed a male predominance of PsA(17-19). Unlike PsA, SLE is known to have much higher prevalence in females relative to males, with 10:1

female: male ratio commonly accepted in the literature(20). It is thus likely that the higher prevalence of SLE that we observed among PsA female patients is due to the female predominance of SLE.

The literature reporting the co-existence of PsA and SLE is scarce.(9, 10) Millns and Muller describe 27 patients with coexistent psoriasis and SLE, 10 of whom were diagnosed with SLE, 13 with discoid lupus erythematosus (DLE) without systemic manifestations of SLE, and 4 with drug-induced SLE or lupus-like syndrome.(8) In a study by Tselios et al., psoriasis was twice as prevalent in SLE patients compared with the general Canadian population.(9) A study by Zalla and Muller showed the most common type of psoriasis associated with SLE to be plaque psoriasis(21). In our literature search, we found a single study showing increased prevalence of PsA among patients with SLE (diagnosed using the American College of Rheumatology Revised Criteria from 1997) in a single tertiary, academic rheumatology specialty clinic in Syracuse, NY, with increase in malar rash, discoid rash, photosensitivity, and arthritis in SLE patients with either co-existing psoriasis or PsA. In this study, it was also noted that antiphospholipid antibody positivity was less common in SLE patients with concurrent psoriasis or PsA(22).

Possible explanations for the increase in SLE prevalence among PsA patients include phototherapy exposure as treatment for psoriasis which may trigger SLE induction(23), as could medications for PsA which increase photosensitivity such as sulfasalazine(8, 10, 21). In our cohort, none of 18 patients with concomitant SLE and PsA had phototherapy treatment prior to SLE diagnosis.

Another possible explanation for the increase in SLE prevalence among PsA patients lies in the high prevalence of comorbidities requiring medications in PsA patients relative to the general population. This higher prevalence of comorbidities among PsA which we found in our study and which was previously described in several studies(24-26) may predispose

them to drug-induced SLE or drug-induced subacute cutaneous lupus erythematosus (SCLE). Of note, in our study, we only included patients fulfilling the 2012 SLICC Classification Criteria for SLE and did not include patients who only had skin manifestations of SLE. We found that the use of possible culprit medications with known potential to induce SLE prior to SLE diagnosis was higher among PsA patients compared to the control group [Table 1]. Using two separate multivariable conditional logistic regression models, we found that PsA patients at higher risk of SLE development were patients diagnosed with PsA at an older age, those with shorter PsA disease duration, or patients on statin therapy. The association between older age of PsA onset and shorter disease duration with SLE development may lie in the higher prevalence of comorbidities found at an older age in general, and in PsA patients in particular, necessitating a larger number and variety of medications in this patient population. Of these, statins in particular (irrespective of particular statin used) are identified as having a significant pharmacovigilant signal associated with SLE development in the World Health Organization Pharmacovigilance Database (VigiBase)(27) with Reporting Odds Ratio (ROR) of lupus-like syndrome of 2.01 (95% confidence interval 1.61-2.51); a similar pharmacovigilant signal is also found in the French Pharmacovigilance Database for all statins except for fluvastatin with ROR of 1.67 (95% confidence interval 1.02-2.74)(28). The higher incidence of hyperlipidemia among PsA patients requiring statin therapy may explain part of the increase in SLE risk among these patients.(3, 24, 25) This higher incidence of statin use among PsA patients can explain why statin use was no longer found to be a risk factor for SLE development in model III where risk of SLE development was calculated out of the entire study population and not only in the PsA patient group as in models I and II.

Anti-TNF therapy, which is commonly used in PsA, can cause drug-induced SLE manifesting primarily with ANA positivity without clinical manifestations of SLE.(6) It is of note that this adverse effect is rare for anti-TNF agents; for instance, in a study by Vaz et al., only 10 out of

760 subjects developed SLE after infliximab treatment.(29) In our study, there was a trend toward lower use of anti-TNF agents in PsA patients with concomitant SLE (27.8%) compared with PsA patients without SLE (36.8%) although it did not reach statistical significance.

Last, the recent implication of interleukin-23 (IL-23) and IL-17, which are known to be associated with psoriasis and PsA,(30, 31) in SLE immunopathogenesis suggests a common underlying pathophysiology for both diseases. For instance, a recent report showed a correlation between elevated IL-17 serum levels and SLE disease activity as well as with higher anti-dsDNA antibody titers; IL-17 blockade was also shown to decrease SLE disease manifestations in animal models(32, 33). Fischer et al. showed elevated IL-23 serum concentrations in SLE patients with high cytokine levels associated with higher atherosclerotic plaque burden, lupus nephritis, and obesity(34).

Our study's limitations consist of the retrospective design which did not capture PsA or SLE disease activity, psoriatic arthritis disease activity, or psoriasis subtype. In addition, as our findings are limited to the Israeli population, as diverse as this population may be, they require validation in other patient cohorts. Moreover, though our study includes data on over 50% of the Israeli population, our study is limited in our finding of a relatively small number of SLE patients within this database. Additionally, we only found a total of 131 matched control PsA patients, which fell short of 10 PsA control patients with similar follow-up time for each of the 18 patients who had PsA with co-existing SLE.

As our risk analysis for SLE development among PsA patients was conducted prior to the publication of the current updated EULAR ACR Classification Criteria for SLE (35), the use of the current criteria relative to the 2012 SLICC Criteria might have impacted our findings. Notably, these criteria require ANA positivity for SLE classification, and in our study, while all of the patients in the control group had a positive ANA, 17/18 (94.4%) in the PsA group with co-existing SLE had ANA positivity.

The strengths of our study lie in using a large database of 4.3 million subjects with long-term follow-up for PsA. Our study is of significance because finding positive correlates between SLE and PsA may advance our understanding of the underlying pathogenesis of both diseases and may affect treatment choices and medication development. Furthermore, the coexistence of these diseases may in turn increase the risk of additional comorbidities such as cardiovascular and metabolic disease, depression, and/or osteoporosis, requiring closer follow-up and preventative medicine in these patients.

In conclusion, our study points to an increase in prevalence of SLE among female PsA patients with patients at highest risk of SLE development being female patients with late-onset PsA, with short disease duration, and especially those of whom are on statin therapy. Clinicians caring for patients with PsA and SLE should be aware of the higher prevalence of comorbid conditions in this patient population. More research is needed to understand the underlying biologic pathway which may be common to SLE and PsA.

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Table 1 - Characteristics of the study population				
		Control	PsA	p- value
Number of patients		24180	4836	-
SLE cases		36 (0.15%)	18 (0.37%)	0.001
Age		56.25+/-15.264	56.31+/-15.244	NS
Sex (Female)		13015 (53.8%)	2603 (53.8%)	NS
Socio-economic status	1	9082 (40.6%)	1552 (32.2%)	<0.0001
	2	8336 (37.3%)	1958 (40.7%)	<0.0001
	3	4956 (22.2%)	1306 (27.1%)	<0.0001
Smokers		9220 (38.3%)	2051 (42.5%)	<0.0001
Ethnicity	Arab	4369 (18.5%)	612 (12.7%)	<0.0001
	Jewish	19296 (81.5%)	4224 (87.3%)	
BMI		27.47+/-5.44	28.65+/-5.803	<0.0001
Comorbidity	Hyperlipidemia	13541 (56%)	3125 (64.6%)	<0.0001
	Hypertension	8383 (34.7%)	2035 (42.1%)	<0.0001
	DM	5339 (22.1%)	1353 (28%)	<0.0001
	Malignancy	2709 (11.2%)	980 (20.3%)	<0.0001
	Osteoporosis	2376 (9.8%)	623 (12.9%)	<0.0001
	Obesity	6790 (28.1%)	1851 (38.3%)	<0.0001
	CHF	758 (3.2%)	218 (4.5%)	<0.0001
	IHD	3000 (12.4%)	766 (15.8%)	<0.0001
	CVA	1312 (5.4%)	304 (6.3%)	0.017
cDMARDs		578 (2.4%)	4090 (84.6%)	<0.0001
bDMARDs	Anti-TNF α	97 (0.4%)	1779 (36.8%)	<0.0001
Possible culprit medication used prior to SLE diagnosis	Statins	5(0.02%)	7 (0.15%)	0.001
	PPI	12 (0.05%)	5 (0.1%)	NS
	BB	1 (0.004%)	2 (0.04%)	0.07-
	ACE-I	7 (0.03%)	1(0.02%)	NS
	Thiazides	7(0.03%)	1 (0.02%)	NS
	Anti-TNFα	0 (0.0%)	2(0.04%)	0.028

ACE-I – Angiotensin Converting Enzyme inhibitors, BB – beta blocker, bDMARDs – Biological Disease Modifying Anti-Rheumatic Drugs, BMI – Body Mass Index, cDMARDs – Conventional Disease Modifying Anti-rheumatic Drugs, CHF – Congestive Heart Failure, CVA – Cerebrovascular Accident, DM- Diabetes Mellitus, IHD – Ischemic Heart Disease, PPI – Proton Pump Inhibitors, NS – Not Significant, PsA – psoriatic arthritis, SLE – Systemic Lupus Erythematosus.

Table 2 - Comparison between SLE patients in the two groups

		<i>Control</i>	<i>PsA</i>	<i>P value</i>
Number of patients		36	18	-
Age		53.67+/-12.88	55.61+/-15.99	NS
Sex (Female)		32 (88.9%)	18 (100%)	NS
Socio-economic status	1	14 (38.9%)	8 (44.4%)	NS
	2	15 (41.7%)	5 (27.8%)	
	3	7(19.4%)	5 (27.8%)	
Smoker		14 (38.9%)	7 (38.9%)	NS
Ethnicity	Arab	7 (19.4%)	3 (16.7%)	NS
	Jewish	29 (80.6%)	15 (83.3%)	
Comorbidity	Hyperlipidemia	16 (44.4%)	9 (50%)	NS
	Hypertension	17(47.2%)	8 (44.4%)	NS
	Diabetes Mellitus	8 (22.2%)	4 (22.2%)	NS
	Malignancy	3 (8.3%)	5 (27.8%)	NS
	Cardiovascular Disease	10 (27.8%)	1 (5.6%)	NS
	Osteoporosis	7 (19.4%)	4 (22.2%)	NS
	Obesity	7 (19.4.5%)	2 (11.1%)	NS
SLE clinical manifestations	Skin	23 (63.9%)	12 (66.7%)	NS
	Oral ulcers	9 (25%)	6 (33.3%)	NS
	Alopecia	9 (25%)	8 (44.4%)	NS
	Arthritis	28 (77.8%)	15 (83.3%)	NS
	Renal	12(33.3%)	4 (22.2%)	NS
	Neurologic	5 (13.9%)	0 (0%)	NS
	Hemolytic anemia	1 (2.8%)	3 (16.7%)	NS
	Leukopenia/ Lymphopenia	21 (58.3%)	9 (50%)	NS
	Thrombocytopenia	9 (25%)	3 (16.7%)	NS

SLE immunologic manifestations	ANA	36 (100%)	17 (94.4%)	NS
	Anti-dsDNA	33 (91.7%)	12 (66.7%)	0.047
	Anti-Sm	10 (27.8%)	5 (27.8%)	NS
	Anti-histone	6 (16.7%)	3 (16.7%)	NS
	ACL	17 (47.2%)	3 (16.7%)	0.038
	Anti-B2GP	10 (27.8%)	4 (22.2%)	NS
	LAC	6 (16.7%)	3 (16.7%)	NS
	Low serum complement	19 (52.8%)	6 (33.3%)	NS
	Positive direct coombs	2 (5.6%)	0 (0%)	NS
	Anti-SSA/SSB	8(22.2%)	6 (33.3%)	NS
Sicca syndrome		9 (25.0%)	4 (22.2%)	NS
Raynaud's phenomenon		7 (19.4%)	3 (16.7%)	NS
RF positivity		5 (12.8%)	3 (16.7%)	NS

ACA – Anti Cardiolipin Antibodies, ANA – Anti Nuclear Antibodies, Anti-B2GP – Anti-Beta 2 Glycoprotein, Anti-dsDNA – anti double-stranded DNA, anti-Sm – anti Smith, Anti-SSA/B-anti-Sjogren's Syndrome-related antigen A/B, CVD – Cardiovascular Disease, LAC – Lupus Anticoagulant, NS – Not Significant, RF – Rheumatoid Factor, SLE – Systemic Lupus Erythematosus.

Table 3 - Comparison within the PsA study group between patients with and without SLE				
		PsA	PsA and SLE	p value
Number of patients		4818	18	-
Age		56.31+/-15.242	54.44+/-15.935	NS
Sex (Female)		2585 (53.7%)	18 (100%)	<0.0001
Socio-economic status	1	1544 (32.2%)	8 (44.4%)	NS
	2	1953 (40.7%)	5 (27.8%)	
	3	1303 (27.1%)	5 (27.8%)	
Smoker		2044 (42.5%)	7 (38.9%)	NS
Ethnicity	Arab	609 (12.6%)	3 (16.7%)	NS
	Jewish	4209 (87.4%)	15 (83.3%)	
Comorbidity	Hypertension	2027 (42.21%)	8 (44.4%)	NS
	Diabetes Mellitus	1347 (28%)	6 (33.3%)	NS
	Malignancy	975 (20.2%)	5 (27.8%)	NS
	CVA	301 (6.2%)	3 (16.7%)	NS
	Osteoporosis	616 (12.8%)	7 (38.9%)	0.005
	Obesity	1847 (38.3%)	4 (22.2%)	NS
cDMARDs		4074 (84.6%)	16 (88.9%)	NS
bDMARDs	Anti TNF- α	1774 (36.8%)	5 (27.8%)	NS
Possible culprit medications inducing SLE	Statins	2741 (56.9%)	9 (50%)	NS
	PPI	3652 (75.8%)	17 (94.4%)	NS
	Beta-blockers	474 (9.8%)	5 (27.8%)	0.027
	ACE-I	2107 (43.7%)	7 (38.9%)	NS
	Thiazides	1044 (21.7%)	4 (22.2%)	NS

ACE-I – Angiotensin Converting Enzyme Inhibitors, bDMARDs – Biological disease-modifying anti-rheumatic drugs, cDMARDs – Conventional disease-modifying anti-rheumatic drugs, CVA – Cerebrovascular Accident, NS – Not Significant, PPI – Proton Pump Inhibitors, PsA – Psoriatic Arthritis, SLE – Systemic Lupus Erythematosus, anti-TNF-Anti-Tumor Necrosis Factor

Table 4: Assessment of risk factors for SLE development in the PsA group

	PsA patient with SLE 18 patients	PsA patients without SLE 131 patients	Univariable model *			Multivariate model 1			Multivariate model 2		
			Odds ratio	CI 95%	p value	Odds ratio	CI 95%	p value	Odds ratio	CI 95%	p value
Age at PsA diagnosis	47.12±18.23	38.9±15.36	1.25	1.09-1.42	0.001				1.25	1.06-1.48	0.008
PsA duration years	2.39±5.33	6.49±7.70	0.86	0.73-1.01	0.06	0.82	0.69-0.98	0.03			
Anti TNF-α	2 (11.1%)	16 (12.2%)	1.22	0.23-6.53	0.82	0.86	0.1-7.29	0.89	0.95	0.1-8.15	0.96
Statins	7 (38.9%)	24 (18.3%)	6.81	1.55-29.84	0.01	12.49	1.73-90.29	0.01	9.86	1.09-89.26	0.042
PPI	5 (27.8%)	56 (42.7%)	0.66	0.20-2.23	0.5	1.17	0.28-4.95	0.83	1.5	0.30-6.70	0.60
Beta Blockers	2 (11.1%)	8 (6.1%)	2.42	0.45-13.09	0.3	4.17	0.53-32.99	0.18	4.76	0.57-39.55	0.150
ACE-I	28 (21.4%)	1 (5.6%)	0.24	0.03-2.03	0.19	0.04	0.001-1.62	0.09	0.34	0.01-2.03	0.10
Thiazides	12 (9.2%)	1 (5.6%)	0.78	7.75	0.83	21.25	0.37-1215.03	0.14	29.60	0.45-1972.72	1.11

ACE-I=angiotensin-converting enzyme inhibitors, Anti-TNF=anti-tumor necrosis factor, CI=confidence interval, PPI=proton pump inhibitors, PsA=psoriatic arthritis, SLE=systemic lupus erythematosus

*Logistic regression was performed separately for each item.
** Multivariate model I- includes psoriatic arthritis duration
*** Multivariate model II- includes age at PsA diagnosis

Table 5: Assessment of risk factors for SLE development in the study population

	Population with SLE	Population without SLE	Univariable model *			Multivariate model III		
			Odds ratio	CI 95%	p value	Odds ratio	CI 95%	p value
Age mean \pm SD	52.76 \pm 13.93	56.26 \pm 15.26	0.99	0.97-1.00	0.09	1.01	0.99-1.03	NS
Sex Female	50 (92.6%)	15568 (53.8%)	10.75	3.88-29.78	<0.0001	11.79	4.25-32.71	<0.0001
Ethnicity Jewish	44 (81.5%)	23476 (82.5%)	0.93	0.47-1.85	NS			
PsA	18 (0.37%)	4818 (99.6%)	2.50	1.42-4.42	0.001	3.68	2.05-6.6	<0.0001
Anti TNF- α	2 (3.7%)	1871 (6.5%)	0.58	0.14-2.29	NS			
Statins	28 (51.9%)	14787 (51.1%)	1.03	0.60-1.76	NS			
PPI	17 (31.5%)	17287 (59.7%)	0.31	0.18-0.55	<0.0001	0.25	0.14-0.46	<0.0001
Beta Blockers	3 (5.6%)	2367 (8.2%)	0.66	0.20-2.12	NS			
ACE-I	8 (14.8%)	10742 (37.1%)	0.30	0.14-0.23	0.001	0.35	0.15-0.79	0.012
Thiazides	8 (14.8%)	5286 (18.3%)	0.78	0.37-1.65	NS			

Medication prescribed before SLE diagnosis

ACE-I=angiotensin-converting enzyme inhibitors, Anti TNF=anti-tumor necrosis factor, CI=confidence interval, NS=not statistically significant, PPI=proton pump inhibitors, PsA=psoriatic arthritis, SLE=systemic lupus erythematosus

*Logistic regression was performed separately for each item.