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Original Scientific Paper

CLINICAL CHARACTERISTICS AND TREATMENT OF LUPUS NEPHRITIS – PRELIMINARY ANALYSIS OF OBSERVATIONAL DATA FROM A NATIONAL REFERRAL CENTRE

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SUMMARY – Lupus nephritis (LN) is one of the most severe features of systemic lupus erythematosus (SLE). Data on LN is scarce in the Croatian population. We analysed the characteristics of LN patients diagnosed at our tertiary referral centre. In this retrospective study, we analysed the following features of patients with biopsy-proven LN diagnosed between 2011 and 2020: demographics, renal laboratory parameters, renal histopathology, and treatment.

A total of 38 patients were included (30 females; mean age 39±15 years). The most common indication for kidney biopsy was proteinuria (89%). The proportion of LN classes was: class I (2.6%), II (5.3%), III (18.4%), IV (42.1%), V (13.2%), III+V (10.5%), IV+V (5.3%). The median time from SLE diagnosis to histologic confirmation of LN was 1.0 year. All patients were treated with methylprednisolone (MP), 68% received MP pulses. Induction treatment included intravenous (IV) cyclophosphamide (CYC) (71%) (15 patients treated per Euro-Lupus and 9 per the National Institutes of Health regimen), oral CYC (3%), or mycophenolate mofetil (11%). 79% of patients received antimalarials. While there is heterogeneity between different populations, our patient profile was similar to that from other European studies. Further follow-up of this group is necessary to assess outcomes in our population.

Key words: *systemic lupus erythematosus, lupus nephritis, treatment, population characteristics*

Introduction

Lupus nephritis (LN), a severe manifestation of systemic lupus erythematosus (SLE), affects around 40 to 50% of SLE patients and can range from silent nephritis (subclinical illness) to end-stage renal disease (terminal illness)[1] Recent studies revealed that the 5- and 15-year risk of ESRD equals 11% and 22%, respectively, and that around 10-30% of LN patients progress to kidney failure requiring renal replacement therapy, with higher percentages being seen in prolif-

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erative LN.[1,2] The clinical course of SLE can vary from benign illness to a rapidly progressive disease with organ failure and death. Patients with SLE have mortality rates ranging from two to five times higher than that of the general population, with renal disease associated with the highest mortality risk.[3,4] SLE patients with renal damage and ESRD have a 14-fold and more than 60-fold, respectively, increased risk of premature death.[5,6] In a study of 10-year mortality from our SLE cohort (2002-2011), LN was associated with a 2.46-fold increased risk of death (odds ratio, 95% confidence interval 1.13-5.37).[7] Biopsy is the key diagnostic procedure in evaluating these patients and histopathology is crucial in determining the classification, management, and prognosis of LN. LN is considered a chameleon of renal pathology, so the histologic classification of LN is required to accurately define the degree of kidney injury associated with SLE, to guide treatment and predict outcomes.[8] The International Society of Nephrology/Renal Pathology Society classification for lupus nephritis (ISN/RPS) published in 2003, reports definitions and classification of glomerular lesions in LN. Lupus nephritis is immune-complex-mediated glomerulonephritis (GN) and is classified into six patterns or classes. In SLE patients with renal injury, it is of great importance to exclude other mechanisms of kidney injury such as thrombotic microangiopathy and lupus podocytopathy which can be seen in up to 24% and 1.3% of LN patients, respectively. The finding of isolated tubulointerstitial nephritis is becoming increasingly recognized.[9,10] A number of studies have found that both SLE and LN show different characteristics and that there might be important heterogeneity in patient characteristics and outcomes, especially in LN which comprises patients with the most difficult clinical course.[11–15] The ALMS study (Aspreva Lupus Management Study) was one of the first studies to systematically explore the potential effect of race/ethnicity on LN treatment. The study reported that race, ethnicity, and geographical region might influence the therapeutic response and that some ethnicities had a varied response to different types of therapy, heralding the future need for personalized treatment.[16,17] Subsequent studies confirmed this concept both in SLE and LN.[13,18] A recent large cross-sectional study enrolling a multiethnic cohort of 1244 SLE patients (48.7% had concurrent LN) of Northern and Southern European, Hispanic, African American, and East Asian descent genotyped for 817,810 single-nucleotide polymorphisms (SNPs) across the genome demonstrated distinct genetic factors which varied with ethnicity and might be responsible for heterogeneity in clinical characteristics and response to therapy.[12] Data on the characteristics of LN patients and therapeutic strategies used in South-Eastern Europe are scarce. Only one well-designed study has been published on the Croatian population thus far, reflecting the diagnostic and therapeutic approach that was currently more than two decades ago.[19] Therefore, the aim of this study is to describe the demographic, clinical, laboratory, and histopathological characteristics and current therapeutic strategies in LN patients in Croatia, using data from the National Referral Centre for SLE.

Subjects and Methods

Subjects

This retrospective study included all adult patients (>18 years of age) with a diagnosis of SLE and a biopsy-proven LN of any class who underwent biopsy in the Kidney Biopsy Unit of our institution, UHC Zagreb, a tertiary, university hospital and in the National referral centre for SLE, between January 2011 and January 2020. All patients met the 1997 revised American College of Rheumatology (ACR) classification criteria for SLE.[20] There were no general or specific exclusion criteria except data completion, i.e., available data on performed biopsy. Kidney biopsy was performed in patients with worsening proteinuria, laboratory signs of decline in kidney function, or active urine sediment presence.[21] For each patient, we obtained and analysed general and disease-specific demographic data at the time of kidney biopsy, as well as 24-hour proteinuria and characteristics of the urine sediment before kidney biopsy. Data obtained from the kidney biopsy specimen was also analysed, as well as treatment regimens used in each patient. All data were obtained during routine patient workup, without the need for any additional examinations. The data are stored in the database of the National Referral Centre for Systemic Lupus Erythematosus and Related Diseases within our institution. Ethical approval for this study was obtained from the Ethical Committee of the

University Hospital Centre Zagreb (02/21 AG). The procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983.

Histopathology

Samples for histological analysis were obtained using the ultrasound-guided percutaneous needle biopsy method, or in some cases, under the control of computed tomography (CT). All adequate samples with renal tissue containing glomeruli were routinely processed for light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). Samples for light microscopy were serially cut and stained with haematoxylin and eosin, periodic acid–Schiff, Mallory trichrome, elastica, and Jones methenamine silver stain. Part of the tissue with glomeruli was frozen, sectioned, and processed for direct immunofluorescence (IF) using immunofluorescent antibodies against IgA, IgG, IgM, C3, C1q fibrinogen, kappa, and lambda light chains. Small cortical tissue pieces with at least one glomeruli were additionally analysed by use of transmission electron microscopy. Kidney biopsies were classified according to the 2003 ISN/RPS criteria system, and activity and chronicity indexes were based according to the scoring system from the National Institutes of Health.[8] The ISN-RPS classification of lupus nephritis is composed of six classes based on glomerular findings and the establishment of patterns of immune complex-mediated glomerular injury, which is the most common form of renal involvement in SLE. Lupus classes are further subdivided using several modifiers such as focal vs. diffuse glomerular involvement, global vs. segmental glomerular injury, as well as whether the glomerular injury is active or chronic. Class I is defined as minimal mesangial lupus nephritis with mesangial immune deposits detected by IF and/or EM but without mesangial hypercellularity on LM. Class II represents mesangioproliferative LN, while classes III and IV denote proliferative forms of lupus nephritis. Class III is defined as focal lupus nephritis involving <50% of affected glomeruli and distinguishes it from class IV, characterized by diffuse glomerulonephritis involving >50% of a total number of glomeruli. Class IV consists of either segmental (class IV-S) or global (class IV-G) involvement and can also have active or sclerotic lesions. Class V stands for membranous lupus nephritis, and class VI for advanced sclerosing lesions affecting >90% of glomeruli. Combinations of membranous and proliferative glomerulonephritis are possible and are classified as either class III and V or class IV and V.[8]

Statistical analysis

Normality was assessed using the D'Agostino-Pearson test. Continuous variables were presented as mean and standard deviation if normally distributed and as median and interquartile range if non-normally distributed. Categorical data were presented as absolute values and proportions. To assess differences between genders, variables were compared between female and male patients with LN. Normally distributed data were compared using Student's t-test and non-normally distributed using Mann-Whitney U-test. The distribution of categorical data across groups was compared using Fisher's exact test. Statistical significance was defined with a two-sided p-value<0.05. Data analysis was done using SPSS v. 23 (IBM Corp., USA).

Results

We have enrolled 38 patients (30 females and 8 males, mean age 37±13 years) with biopsy-proven LN. When examining the time of onset of LN, i.e., early-onset (patients diagnosed within <5 years following diagnosis) vs. late-onset LN, 75% had early-onset and 25% had late-onset LN. There was no difference in time from diagnosis of SLE to confirmation of LN or the proportion of patients having LN diagnosis in the first year of SLE (males vs. females, 50% vs. 53%, respectively, p=0.77). Demographic and clinical characteristics and comparison between females and males are presented in Table 1. The most common indication for kidney biopsy was proteinuria (89%), followed by a decline in kidney function (8%), and glomerular haematuria (3%). Mean proteinuria at the time of biopsy was 4.2±3.1 g/day and ranged from 0.1 to 10.8 g/day. There was no statistical significance in the frequency of nephrotic proteinuria between genders (females vs. males, 43% vs. 63%, p=0.44), but males tended to have non-significantly higher proteinuria (females vs. males, 3.8±3.0 vs. 5.6±3.5, respectively, p=0.14). A total of 20 (53%) patients had non-nephrotic proteinuria (<3.5 g/day, of which 3 patients with proteinuria<500 mg/day) and 18 (47%) had nephrotic proteinuria. The median time from SLE diagnosis to histologic confirmation of

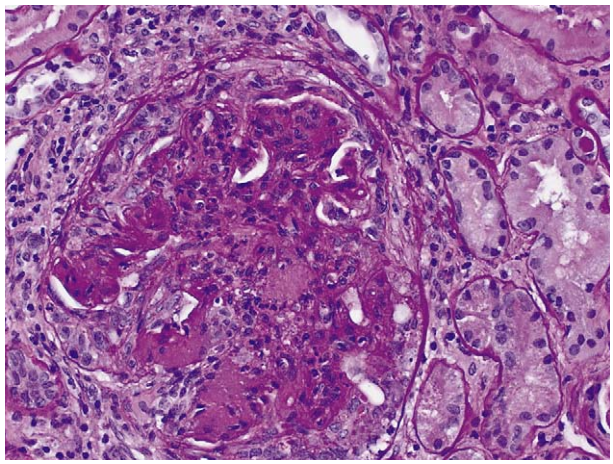

Figure 1. Glomerulus with mesangial hypercellularity, global endocapillary proliferation and fibrocellular crescent in LN Class IV (PAS stain, magnification 200x).

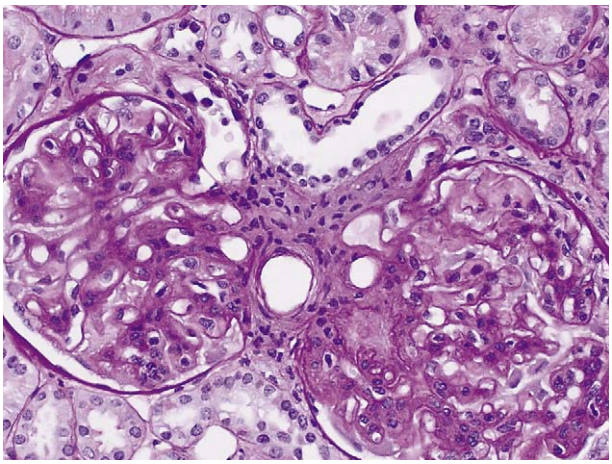

Figure 2. Segmental endocapillary proliferation and thickening of glomerular basal membranes in LN class III-V (PAS stain, magnification 200x).

Table 1. Demographic and clinical characteristics of the group and comparison between females and males.

Characteristic	Whole group (N=38)	Females (N=30)	Males (N=8)	p*
Age at diagnosis of LN (years)	37±13	37±13	37±12	0.97
Age at diagnosis of SLE (years)	33±14	32±14	34±15	0.75
Time from diagnosis of SLE to LN (years)	4.4±6.7 1 (0 - 5.5)	4.4±6.8 1 (0 - 6)	4.0±6.7 1 (0 - 5)	0.84
Indication for biopsy				0.76
Proteinuria	34 (89)	27 (90)	7 (88)	
Decline in kidney function	3 (7)	2 (7)	1 (12)	
Glomerular hematuria	1 (3)	1 (3)	0 (0)	
LN Class				0.88
I	1 (2.6)	1 (3.3)	0 (0)	
II	2 (5.3)	2 (6.7)	0 (0)	
III	7 (18.4)	6 (20.0)	1 (12.5)	
IV	16 (42.1)	13 (43.3)	3 (37.5)	
V	5 (13.2)	2 (6.7)	3 (37.5)	
III+V	4 (10.5)	4 (13.3)	0 (12.5)	
IV+V	2 (5.3)	2 (6.7)	0 (0)	
VI	0 (0)	0 (0)	0 (0)	
Unclassified	1 (2.6)	0 (0)	1 (12.5)	
Induction therapy				0.80
Cyclophosphamide + MP	28 (74)	24 (80)	4 (50)	
MMF + MP	6 (16)	4 (13)	2 (25)	
Other	3 (8)	2 (7)	1 (12.5)	
None	1 (2)	0 (0)	1 (12.5)	

*p-value for comparison between males and females; values present either absolute count (percentage), mean ± standard deviation or median (interquartile range); MP – methylprednisolone, MMF – mycophenolate mophetil, SLE – systemic lupus erythematosus, LN – lupus nephritis

LN was 1.0 year (IQR 0.0 to 5.25 years, mean 4.4±6.6 years). Prevalence among LN classes was: class I (2.6%), II (5.3%), III (18.4%), IV (42.1%), V (13.2%), III+V (10.5%), IV+V (5.3%) and unclassified (2.6%) (Figures 1 and 2; Table 1). Patients were treated with cyclophosphamide iv. + methylprednisolone (74%), cyclophosphamide po. + methylprednisolone (3%), MMF + methylprednisolone (16%), other or none (10%). Among the patients treated with intravenous cyclophosphamide, 15 patients received induction per Euro-Lupus (i.e., six bi-weekly applications of 500 mg cyclophosphamide) and 9 per the NIH regimen (i.e., six-monthly applications of 1000 mg cyclophosphamide). A total of 68% of patients received methylprednisolone pulses (≥250 mg, for three subsequent days). The average cumulative dose of cyclophosphamide was 4048±1934 mg. When looking at maintenance therapy, all patients received oral corticosteroids combined with MMF (47%), azathioprine (14%), cyclophosphamide (14%), cyclosporine (11%), rituximab (3%), and other immunosuppressants (11%). A total of 79% of patients received antimalarial drugs. Eight patients received immunoglobulins and two underwent therapeutic plasma exchange.

Discussion

This retrospective study aimed to present demographic and clinical characteristics of LN patients from Croatia. Our patients were predominantly females (79%), which is in line with studies conducted worldwide, including United States[22], Spain[23], Serbia[24], Taiwan[25], Brazil[26], India[27]. Conversely, studies conducted in cohorts of patients with LN did not have such a pronounced female predominance. Compared to the male to female ratio in the overall population of SLE patients, a relatively higher proportion of males was reported in most of the large LN cohorts (male vs. female, 27–75% vs. 16–52%, respectively; male-to-female ratio ranging from 1.1:1 to 1.7:1). Interestingly, the male to female ratio has not been shown to vary with ethnicity.[28–32] It seems that males exhibit a higher risk of renal affection, despite the overall higher proportion of females being afflicted by SLE in general.[33] The mean age of our LN patients was 37 years (ranging from 19 to 64 years), which is consistent with a large Medicaid-based study on adult SLE patients, which reported that 50.1% of patients were aged 30 to 49 years and 91.8% were aged 18 to 49 years. Compared to patients with lupus nephritis, the whole group of SLE patients was somewhat older and aggregating less in the 18 to 29 age group (LN vs. SLE, 41.7% vs. 27.7%, respectively).[34] A large international multiethnic cohort also reported a relatively young age at onset of LN (31.3 years)[33], as did a Spanish study of 933 patients with LN (28.4 years).[23] Several further studies also reported younger age at diagnosis of LN when compared to the age at diagnosis of non-nephritic SLE.[33,35,36] In our group, LN was most commonly confirmed in the first year after SLE diagnosis (17 out of a total of 34 patients with a known year of both SLE and LN diagnosis), however with a wide time range and a mean time from diagnosis of SLE to confirmation of LN of 4.4 years. The findings of several studies are in line with this observation of LN presenting early in the disease course of SLE. Galindo-Izquierdo et al. reported that 56.3% of patients had LN diagnosed in the first year following SLE onset[23], while Seligman et al. identified a gender-specific difference with a higher proportion of males reaching the diagnosis of LN in the first year (males vs. females, 47% vs. 20%, respectively).[37] We were not able to confirm a gender-specific difference in this aspect (females vs. males, 50% vs. 53%). A very recent study by Delfino et al. aimed to identify differences between early-onset LN (defined as LN occurring within <5 years from diagnosis of SLE) and late-onset LN (diagnosis of LN after ≥5 years of SLE diagnosis). The study found that the majority of LN occurred early (70.4%) but identified no difference in disease characteristics or treatment outcomes.[38] In our study, 75% of LN patients were diagnosed within <5 years following diagnosis of SLE, and it will be interesting to explore the differences in outcomes of early- vs. late-onset patients in the further studies on our group of patients. Proteinuria was by far the most frequent indication for kidney biopsy in our group. All patients had at least mild proteinuria, and almost half of them had nephrotic range proteinuria. There was no difference in the degree of proteinuria or the frequency of nephrotic range proteinuria between males and females. However, while not statistically significant, males in our study had a trend towards higher proteinuria (females vs. males, 3.8 vs. 5.6 g/day, respectively). Yong et al. reported a similar finding in an Australian cohort when examining indications for renal biopsy: 85% of patients had

proteinuria, including 23% with nephrotic range proteinuria.[39] Resende et al. reported values of proteinuria in males similar to the values observed in our group (5.3 g/day).[40] In a Chinese cohort of 1814 patients with biopsy-proven LN, proteinuria at the time of biopsy was 3.08 g/day with higher values in males (females vs. males, 2.93 vs. 3.99 g/day). A total of 30.9% of patients had nephrotic range proteinuria at the time of biopsy, while 21.7% had impaired kidney function and 5.1% had gross hematuria.[41] A relatively small proportion of our patients had insignificant (low-grade) proteinuria (<0.5 g/day). A very recent study by De Rosa et al. comparing 46 patients with (insignificant) proteinuria of <0.5 g/day and 176 patients with proteinuria of higher range at the time of biopsy reported that prevalence of class III was higher in the insignificant proteinuria group (insignificant vs. high proteinuria group, 30.4% vs. 10.2%, respectively). Conversely, class IV was less prevalent in the insignificant proteinuria group (45.7% vs. 76.6%, respectively).[42] The study accentuated the surprisingly high prevalence of proliferative LN in patients with insignificant proteinuria. This is complementary to the findings of Zabaleta-Lanz et al. demonstrating that silent LN (a distinct entity from LN with low proteinuria as defined in the study by De Rosa et al.) might also have a proliferative histopathology, albeit less frequently than in overt disease, and is probably the earliest stage of LN.[43] In a study by Mavragani et al., almost a quarter of patients with proliferative LN (classes III and IV) (24.1%) had insignificant proteinuria (<0.5 g/day).[44] While the small number of patients with proteinuria of <0.5 g/day in our group precluded us from conducting a thorough analysis of the relationship of low proteinuria with histopathology, the three patients with low proteinuria had LN class I, II and III+V, respectively. Based on these results, it should be noted that low proteinuria at the time of biopsy does not exclude proliferative LN or significant renal injury in general. Therefore, an active urinary sediment (especially with urinary casts) should probably be viewed as an equally important indication for renal biopsy as proteinuria.[45]

With regard to histopathology, over 60% of our patients had proliferative LN (classes III and IV), with class IV predominance. This is consistent with several large studies. Hanly et al. examined 377 renal biopsies of patients with LN, revealing that 70% had classes III and IV with classes V, II, I, and VI following in order of descending frequency.[33] Data from a large Chinese cohort similarly revealed 52.7% of patients with LN classes III and IV, with other classes being less common.[41] A recent Japanese study reported 53.8% of patients with class III and IV, as well as 22.2% with class V.[46] The vast majority of our LN patients were treated with a cyclophosphamide-based induction regimen. Patients with a severe clinical presentation and profound proteinuria were treated according to the NIH induction regimen, while others underwent induction either with the Euro-Lupus or the MMF-based regimen. The higher proportion of patients treated as per the Euro-Lupus regimen compared to the NIH regimen is in line with other studies and reflects the notion that lower-dose cyclophosphamide is as equally effective as higher dose regimens, yet with less short-term and long-term toxicity.[47–50] Possible reasons for the relatively low proportion of patients treated with MMF is the relatively higher cost of this medication and its consequently lower availability in our routine setting, especially in the first half of the observed period (2011-2015). Furthermore, the use of intravenous cyclophosphamide is less associated with the issue of patient compliance.[51] Our study had several limitations. This was a retrospective study with all limitations and risk of bias inherent to this study type. With the current data analyzed in this study, we were not able to assess patients' outcomes. The sample size was relatively small, although comparable to a number of studies, and, given that the sample was obtained in a tertiary hospital, it might not be representative of all LN patients. However, our hospital is the national referral center for SLE and treats both self-referred and physician-referred patients across the country. On the other hand, this is a pilot study aiming to describe the population of our LN patients over a limited time period. The identification of our LN cases was limited to finding patients that underwent renal biopsy at our nephrology unit, possibly omitting patients who underwent kidney biopsy at another facility. Furthermore, this was mainly a descriptive study with no comparator group.

Conclusion

We have presented the main characteristics of our group of patients with LN diagnosed over a 10-year period. While there is significant heterogeneity be-

tween different populations of LN patients, our patient profile was similar to that from a number of European studies. This study will serve as a foundation for defining a retrospective cohort of LN patients, allowing us to assess disease and renal-specific outcomes of patients from one of the largest referral centers in Southeast Europe.

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Sažetak

KLINIČKE KARAKTERISTIKE I LIJEČENJE LUPUSNOG NEFRITISA – PRELIMINARNA ANALIZA OPSERVACIJSKIH PODATAKA NACIONALNOG REFERENTNOG CENTRA

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Lupusni nefritis (LN) je česta i vrlo ozbiljna manifestacija sustavnog eritemskog lupusa (SLE). Još uvijek nema dovoljno podataka o karakteristikama bolesnika s LN u Hrvatskoj. Analizirali smo karakteristike bolesnika s LN koji su liječeni u referentnom centru naše tercijarne ustanove. U ovu retrospektivnu studiju uključili smo bolesnike s biopsijom potvrđenim LN u periodu od 2011. do 2020. godine, analizirali smo demografske podatke, parametre bubrežne funkcije, patohistološki nalaz bioptata bubrega i liječenje. U studiju je uključeno 38 bolesnika (30 žena, prosječna dob 39±15godina). Najčešća indikacija za biopsiju bubrega bila je proteinurija (89%). Raspodjela klasa LN bila je sljedeća: klasa I(2,6 %), II(5,3 %), III(18,4 %), IV(42,1 %), V(13,2 %), III+V(10,5 %), IV+V(5,3 %). Prosječno vrijeme od dijagnoze SLE do histološke potvrde LN bilo je 1,0 godina. Svi bolesnici su liječeni kortikosteroidima, 68 % liječeno je bolusima metilprednizolona. Indukcijska terapija uključivala je parenteralnu primjenu ciklofosfamida (CYC) (71 %) (15 bolesnika liječeno je prema Euro-lupus protokolu, 9 bolesnika prema protokolu Nacionalnog instituta za zdravlje (NIH)), peroralni CYC (3 %) ili mikofenolat mofetil (11 %). Antimalarike je primilo 79 % bolesnika. Unatoč heterogenosti između različitih populacija s LN, profil bolesnika uključen u ovu studiju sličan je ostalim europskim studijama. Daljnje praćenje potrebno je da bi se istražili ishodi u ovoj populaciji.

Ključne riječi: *sustavni eritemski lupus, lupus nefritis, liječenje, karakteristike populacije*