The long-term outcomes and histological transformation in class II lupus nephritis

Abdulkareem O. Alsuwaida, FRCPC, MSc, *Amaar A. Bakhit,* MRCP (UK), SBIM, *Feras A. Alsuwaida,* Ms, *Junaid J. Wadera,* MD, MPH, *Hala M. Kfoury,* MD, FRCPA, *Sufia Husain,* MD, FRCPath.

ABSTRACT

الأهداف: هناك اختلاف في كيفية علاج التهاب الكلية بالذئبة الحمراء من الدرجة الثانية . قمنا بفحص النتائج السريرة و المخبريه لالتهاب الذئبة الحمراء الكلوي من الدرجة الثانية .

الطريقة: شملت هذه الدراسة المرضى الذين يعانون من التهاب الكلى بالدرجة الثانية بالذئبة الحمراء وتم أخذ خزعة الكلى الأولى من يناير 1996 وحتى ديسمبر 2016 في مستشفى الملك خالد الجامعي بالرياض. تم فحص معدل التعافي الكامل، تدهور وظيفة الكلى، والتحول النسيجي في الخزعة الثانية للكلية.

النتائج: شملت الدراسة 32 مريضا من الإناث وكان العرض الأكثر تكرارا (٪62.5 من المرضى) بيلة دموية مع نسبة بسيطة من الزلال. وقد لوحظ إصابة الكلى بالاعتلال الحاد في ٪22 من المرضى، و ٪9.4 لديهم زلال بكميات كبيره. بأستخدام الكورتيزون فقط في 25 مريضه أدى الى الاستجابة الكاملة في٪92 . بعد المتابعة بمتوسط 8 سنوات، تزايد مستوى الكرياتينين الى الضعف. تم إجراء خزعة ثانية في 17 مريضا (٪53)، ولوحظ التحول إلى فئات أخرى من التهاب الكلى في ٪65 من هؤلاء المرضى.

الخاتمة: وأظهرت دراستنا أن العلاج بالكورتيزون قد يكون العلاج المناسب للدرجة الثانية من التهاب الذئبة الحمراء الكلوي في حال كانت كميات الزلال في البول بسيطة ووظائف الكلى في المستوى الطبيعي. المرضى الذين يعانون من كميات زلال عالية او اعتلال في وظائف الكلى فقد يتطلب العلاج أستخدام المزيد من ألادوية المثبطة للمناعة .

Objectives: To examined the short and long-term outcome of class II lupus nephritis (LN).

Methods: This retrospective study included patients with class II LN at their first renal biopsy between January 1996 and December 2016 in King Khaled University Hospital, Riyadh, Saudi Arabia. The rate of complete remission, worsening renal function, and histological transformation in the second biopsy were examined.

Results: The study included 32 female patients with class II LN. The most frequent presentation (62.5% of patients) was hematuria with subnephrotic range proteinuria. The clinical presentation included acute kidney injury in 22% of patients, and 9.4% had nephrotic range proteinuria. Management with steroid monotherapy in 25 patients resulted in complete remission for 92% of these patients at 6 months. After a median follow up of 8 years, 2 patients had a doubling of their serum creatinine. During the follow up 17 patients (53%) needed a second biopsy, which revealed transformation to other classes (65%).

Conclusions: Daily steroid monotherapy may be an appropriate first-line treatment for class II LN that presents with subnephrotic range proteinuria and normal kidney function. Patients with acute kidney injury and/or nephrotic range proteinuria may warrant more aggressive immunosuppressive regimens.

Saudi Med J 2018; Vol. 39 (10): 990-993
doi: 10.15537/smj.2018.10.22435

From the Department of Internal Medicine (Alsuwaida A, Bakhit, Alsuwaida F, Wadera) and the Department of Pathology and Laboratory Medicine (Kfoury, Husain), College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia.

Received 13th March 2018. Accepted 13th August 2018.

Address correspondence and reprint request to: Dr. Abdulkareem Alsuwaida, Department of Internal Medicine, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia. E-mail: suwaida@ksu.edu.sa
ORCID ID: orcid.org/0000-0001-5470-5557

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that involves different organs of the body; one of these major organs is the kidney, which causes lupus nephritis (LN). Between 25% and 50% of SLE patients will have evidence of LN at disease onset, and up to 60% may later develop renal disease, which is considered to be a major contributor to morbidity and mortality.[1,2] Patients with class II

LN have excellent prognosis and outcomes compared to other classes (III, IV, and V).[3] However, there are discrepancies in the guidelines on the treatment of class II LN due to a lack of evidence. Most of the guidelines published in the National Library of Medicine recommend hydroxychloroquine alongside renin-angiotensin-aldosterone system (RAAS) inhibitors to manage proteinuria.[4-6] The role of immunosuppression management in International Society of Nephrology/Renal Pathology Society (ISN/RPS)- defined class II LN is less clear. Moreover, patients with LN class II are at higher risk of histological transformation compared to other ISN/RPS classes,[7] which might change their prognosis and disease management.[8-11] The main objective of this study is to assess how patients with LN class II respond to immunosuppressive therapy, their long-term prognosis and their histological transformation to other ISN/RPS classes in a repeated biopsy.

Methods. This retrospective study includes patients who received a diagnosis of LN class II on their first renal biopsy between January 1996 and December 2016 in accordance with the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification[7] at King Khalid University Hospital in Riyadh, Saudi Arabia. All patients with diagnosis of SLE and had a native kidney biopsy were included. Only patients with incomplete records were excluded. The biopsies were re-evaluated by 2 renal pathologists blinded to the clinical data. This study retrospectively reviews medical records of patients who have been diagnosed with LN and data were recorded for standard clinical purposes. To protect confidentiality, data were analyzed and reported in a de-identified, aggregate form. The study was approved by the Institutional Review Board (IRB) at King Saud University (E-12-811) and no patient consent was collected.

Demographic, clinical and histological data were analyzed. The clinical data included the initial presentation to the nephrologist and symptoms of SLE (photosensitivity, arthritis, oral ulcers, serositis, and malar, renal, cerebral, hematological and discoid rashes). Laboratory data including urine sediments, urine protein, and complement (C3, C4), were collected at the time of diagnosis, first biopsy, 6 months after the first renal biopsy and last follow-up. The Standard Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score was used at the time of the kidney biopsy to assess the disease activity.[12] At the first renal biopsy and during follow-up, patient medications, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCB), beta blockers, statin, glucocorticoids and immunosuppressant agents (Tacrolimus, Cyclosporine, Mycophenolate Mofetil and Cyclophosphamide), were recorded.

Patients were considered to have complete remission if proteinuria was less than 0.3 gm per day and creatinine was normal at 6 months after the biopsy.[13] Worsening renal function was defined as a doubling of the baseline serum creatinine at the last follow-up.

For the patients who underwent a second biopsy, the following data were collected: time between the first and second biopsy, reason for the second biopsy (increasing proteinuria, worsening serum creatinine, active lupus) and histological transformation to another class of LN in the second biopsy. The research was in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of King Khaled University Hospital in Riyadh, Saudi Arabia.

Statistical analysis. Statistical analyses were carried out using the Statistical Package for the Social Science (SPSS version 24) software (Armonk, NY: IBM Corp.). Categorical variables are reported as absolute number and percent, and the continuous variables are given as the mean ± SD. We compared serum creatinine at baseline and the last follow-up visit for each patient. The endpoint for renal survival was defined as a doubling of serum creatinine or ESRD. $P \leq 0.05$ was considered significant.

Results. The study included 61 patients with SLE (59 female and 2 male) and class II LN. Twenty-nine patients were excluded due to missing data. The remaining 32 female patients had a mean age of 31.2 years at diagnosis with LN (**Table 1**). Hematuria with subnephrotic range proteinuria in 20 (62.5%) patients was the most frequent presentation, and 5 of these 20 had a gross hematuria. Subnephrotic-range proteinuria was seen in 8 patients, while 4 patients had a nephrotic range proteinuria (**Table 2**). Elevated blood pressure was observed in 7 patients (22%), and acute kidney injury (AKI) was also noted in 7 patients (22%). The median serum creatinine and proteinuria at diagnosis were 78 µmol/l (normal creatinine levels in women range from 60-110 µmol/L) and 0.8 gm per day (normal urinary protein excretion is <150 mg/24 hours), respectively.

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Anti-double-strand DNA antibodies were positive in 22 patients (68.75%), and low complements were observed in 11 patients (34.4%).

The prescribed medications were steroid monotherapy in 25 patients (78%), steroid and Mycophenolate Mofetil in 6 patients (18.8%), and steroid and Cyclophosphamide in one patient. The 25 patients treated with prednisolone alone had a median dosage of 60 mg per day (0.5-1 mg/kg), and complete remission at 6 months was seen in 23 patients (92%). Among those with abnormal serum creatinine at initial presentation, 4 patients had normalized serum creatinine, 2 had partial remission, and one had worsening renal function.

A second biopsy was carried out in 17 patients (53%). The reason for the repeated biopsy was an increase in proteinuria in 9 patients (53%), SLE flare with abnormal urine analysis in 5 patients (29.4%) and an increase in serum creatinine in 3 patients (17.6%). The median duration between the first and second biopsy was 5.5 years. The repeated biopsy showed transformation to other classes in 11 patients (64.7%): 5 patients transformed to class III, 4 patients transformed to class IV and 2 patients transformed to class VI (**Table 3**). After a median follow up of 8 years, renal function worsened in 2 patients.

Table 1 - Demographics and laboratory values in the 32 systemic lupus erythematosus patients with class II lupus nephritis at time of first biopsy.

Demographic and laboratory	Values
Age, mean, years	31.2
BMI, kg/m², (mean±SD)	26.6 ± 6.2
Patients with diabetes, n (%)	3 (9.3)
Anti-DNA positive patients, n (%)	22 (68.8)
Hb, (mean±SD), g/dL	9.97 ± 2.19
Platelet count, (mean±SD), x 10^9/L	218.44 ± 89.69
WBC count, (mean±SD), x 10^9 per liter	5.4 ± 3.24
24 hour urine protein, (mean±SD), g/d	1.77 ± 2.5
Urine WBC, (mean±SD), n/hpf	8.61 ± 2.3
Urine RBC, (mean±SD), n/hpf	8.89 ± 2.14
Creatinine, mean (SD), µmol/L	100.24 ± 59.46
Urea, (mean±SD), mmol/L	6.33 ± 4.2
ESR, (mean±SD), mm/hr	83.95 ± 27.42
Low C3, n (%)	5 (15.6)
Low C4, n (%)	6 (18.7)
Albumin, (mean±SD), g/L	28.32 ± 9.47
SLEDAI-2K, (mean±SD)	16.76 ± 4.39

BMI - body mass index, DNA - double-stranded DNA, Hb - hemoglobin, WBC - white blood count, ESR - erythrocyte sedimentation rate, C3 - complement 3, C4, complement 4

Table 2 - Clinical presentation in the 32 systemic lupus erythematosus patients with class II lupus nephritis at time of first biopsy.

Clinical presentations	n (%)
Subnephrotic range proteinuria alone	8 (25.0)
Hematuria with subnephrotic range proteinuria	20 (62.5)
Gross hematuria	5 (15.6)
Nephrotic syndrome	4 (12.5)
Elevated serum creatinine	7 (21.9)

Table 3 - International Society of Nephrology/Renal Pathology Society (ISN/RPS) classifications on repeat biopsy among 17 patients with Class II.

ISN/RPS classifications	n (%)
ISN/RPS II	6 (35.3)
ISN/RPS III	5 (29.4)
ISN/RPS IV	4 (23.5)
ISN/RPS VI	2 (11.8)

Discussion. Although LN class II is considered a mild disease, one-fifth of patients present with serious disease. The most common clinical presentations of LN II are microscopic hematuria with subnephrotic range proteinuria and normal serum creatinine;[1,3,8] however, other reports have shown that those with initial presentation of LN class II might have nephrotic range proteinuria.[14] The heavy proteinuria possibly relates to podocytopathy, as the histological changes are not sufficiently severe to explain this degree of proteinuria. Our study also showed that patients with LN II may present with abnormal kidney function.

Although LN class II is considered a benign disease, our studies have shown that it is not always associated with favorable outcomes.[3,10] The long-term outcomes depend on the initial clinical presentation, the response to therapy and the histological transformation (HT) to another class.

In our study, HT occurred in 11 patients (34.4%), which is comparable to results of other studies. Predicting those patients who will progress to other classes will help clinicians define the optimal time to begin therapy and increase remission rates. Collado et al[11] showed HT in 17 patients (41.4%) in a study of Argentine patients with LN class II. Pakozdi et al[8] reported a rate of HT of 63% in patients with LN class II. The frequency of HT in LN class II reinforces the concept that mesangial LN can be considered the beginning of a disease spectrum that starts in the mesangium and then progresses to involve other parts of the glomerulus.[15] Moreover, there is a discrepancy among the guidelines on the use of the immunosuppressing agents for Class II LN.[4,6] In our study, we observed complete remission in 23 patients

(92%) of those treated with prednisolone alone at a dosage of 0.5-1 mg/kg. Collado et al[11] reported that 70% of their patients responded to treatment with corticosteroids at a dosage of 0.5 to 1 mg/kg per day. A lower rate of remission was also observed in the study carried out by Collado et al,[11] in which 29% of the 34 patients with LN class II were in complete remission at one year. Clinicians may need to consider the initial clinical presentation of patients with class II LN. Patients with nephrotic range proteinuria or abnormal serum creatinine may need to be treated with more aggressive immunosuppressive therapy similar to those patients with class III or IV LN.

This study has several limitations. Retrospective methodologies are vulnerable to lost data and particularly to the loss of follow-up information. In addition, the study consists of a relatively small sample of LN biopsies. Despite these limitations, it is hypothesized that underestimating class II LN may have deleterious effects, specifically for patients with abnormal serum creatinine or advanced proteinuria. Individualizing treatment decisions and increasing immunosuppressive therapy among those patients who fail to reach complete remission on steroid monotherapy will be the best strategy until more evidence is available.

In conclusion, our study shows that class II LN carries a significant risk of histological transformation in subsequent kidney biopsies, which might affect the patient's outcome and prognosis. Daily steroid use as monotherapy may have potential therapeutic benefit; thus, could be considered for randomized controlled trial to prove its efficacy as the first line agent. Patients with ISN/RPS class II with AKI and/or nephrotic range proteinuria may warrant more aggressive immunosuppressive treatment similar to ISN/RPS III or IV. Larger prospective trials are needed to validate this strategy and identify those patients who are less likely to obtain remission.

Acknowledgment. *We would like to thank American Journal Experts for English language editing.*

References

1. Teh CL, Phui VE, Ling GR, Ngu LS, Wan SA, Tan CH. Causes and predictors of mortality in biopsy-proven lupus nephritis: the Sarawak experience. ***Clin Kidney J*** 2018; 11: 56-61.
2. Hanly JG, O'Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. ***Rheumatology (Oxford)*** 2016; 55: 252-262.
3. Dall'Era M, Cisternas MG, Smilek DE, Straub L, Houssiau FA, Cervera R, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis Cohort. ***Arthritis Rheumatol*** 2015; 67: 1305-1313.
4. Wilhelmus S, Bajema IM, Bertsias GK, Boumpas DT, Gordon C, Lightstone L, et al. Lupus nephritis management guidelines compared. ***Nephrol Dial Transplant*** 2016; 31: 904-913.
5. Tunnicliffe DJ, Singh-Grewal D, Kim S, Craig JC, Tong A. Diagnosis, Monitoring, and Treatment of Systemic Lupus Erythematosus: A Systematic Review of Clinical Practice Guidelines. ***Arthritis Care Res (Hoboken)*** 2015; 67: 1440-1452.
6. Muangchan C, van Vollenhoven RF, Bernatsky SR, Smith CD, Hudson M, Inanç M, et al. Treatment Algorithms in Systemic Lupus Erythematosus. ***Arthritis Care Res (Hoboken)*** 2015; 67: 1237-1245.
7. Bajema IM, Wilhelmus S, Alpers CE, Bruijn JA, Colvin RB, Cook HT, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. ***Kidney Int*** 2018; 93: 789-796.
8. Pakozdi A, Pyne D, Sheaff M, Rajakariar R. Utility of a repeat renal biopsy in lupus nephritis: a single centre experience. ***Nephrol Dial Transplant*** 2018; 33: 507-513.
9. Narváez J, Ricse M, Gomà M, Mitjavila F, Fulladosa X, Capdevila O, et al. The value of repeat biopsy in lupus nephritis flares. ***Medicine (Baltimore)*** 2017; 96: e7099.
10. Tannor EK, Bates WD, Moosa MR. The clinical relevance of repeat renal biopsies in the management of lupus nephritis: a South African experience. ***Lupus*** 2018; 27: 525-535.
11. Collado MV, Dorado E, Rausch S, Gomez G, Khoury M, Zazzetti F, et al. Long-term Outcome of Lupus Nephritis Class II in Argentine Patients: An Open Retrospective Analysis. ***J Clin Rheumatol*** 2016; 22: 299-306.
12. Castrejón I, Tani C, Jolly M, Huang A, Mosca M. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. ***Clin Exp Rheumatol*** 2014; 32 (5 Suppl 85): S85-S95.
13. Subspecialty Group of Renal Diseases, the Society of Pediatrics, Chinese Medical Association. Evidence-based guideline on diagnosis and treatment of lupus nephritis (2016). ***Zhonghua Er Ke Za Zhi*** 2018; 56: 88-94.
14. Tang Y, Zhang W, Zhu M, Zheng L, Xie L, Yao Z, et al. Lupus nephritis pathology prediction with clinical indices. ***Sci Rep*** 2018; 8: 10231.
15. The clinical significance of serial kidney biopsies in lupus nephritis. Abdulkareem O. Alsuwaida. ***Mod Rheumatol*** 2014; 24: 453-456.