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EVALUATION OF CLINICAL AND PATHOLOGICAL FINDINGS AND TREATMENT OUTCOMES OF PATIENTS WITH LUPUS NEPHRITIS: A SINGLE CENTRE EXPERIENCE

LUPUS NEFRİTLİ HASTALARIN KLİNİK VE PATOLOJİK BULGULARININ DEĞERLENDİRİLMESİ VE TEDAVİ SONUÇLARI: TEK MERKEZ DENEYİMİ

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ABSTRACT

Objective: Renal involvement in systemic lupus erythematosus (SLE), also known as lupus nephritis (LN), leads to a worse prognosis than SLE without kidney involvement.

Material and Methods: Biopsy-proven LN patients diagnosed between January 2012 and January 2021 were reviewed. Complete remission (CR) was defined as a reduction in the urinary protein-to-creatinine ratio (UPCR) below 0.50 g/g. Partial response is characterised by a 24-h urine protein excretion reduction to below 3 g/day with at least a 50% decrease in proteinuria. Primary effective renal response was defined as PCR of less than 0.7 g/g and the absence of any rescue therapy for treatment failure.

Result: All patients exhibited proteinuria at diagnosis, with class IV LN being the most common (36.4%) form, and 65.9% had proliferative LN. At 12 months, CR was achieved in 16 patients (37.2%) with significant differences in systolic and diastolic blood pressure and eGFR at diagnosis (p=0.01, p=0.02, and p=0.016, respectively). CR rates were lower at 12 months in patients with proliferative LN (p=0.024) and interstitial inflammation (p=0.04). Besides, no significant difference was found in CR rates at 6 and 12 months between PLN patients treated initially with steroids and cyclophosphamide and those treated with steroids and mycophenolate mofetil (p>0.05). However, the median time to achieve CR was shorter in the mycophenolate mofetil group (p=0.048).

ÖZET

Amaç: Sistemik lupus eritematozusun (SLE) böbrek tutulumu olarak bilinen lupus nefriti (LN), böbrek tutulumu olmayan SLE'ye göre daha kötü bir prognoza yol açar.

Gereç ve Yöntem: Ocak 2012 ile Ocak 2021 arasında tanı konulan biyopsiyle kanıtlanmış LN hastaları incelendi. Tam remisyon (TR), idrar protein-kreatinin oranının (PKO) 0,50 g/g'nin altına düşmesi olarak tanımlandı. Kısmi yanıt, 24 saatlik idrar protein atılımının günde 3 g/günün altına düşmesi ve proteinüride en az %50 azalma olarak tanımlandı. Birincil etkili renal yanıt ise 0,7 g/g'dan düşük PKO ve tedavi başarısızlığı için herhangi bir kurtarma tedavisinin olmamasıdır.

Bulgular: Tanı anında tüm hastalarda proteinüri mevcut olup, en yaygın form %36,4 ile sınıf IV LN idi ve hastaların %65.9'unda proliferatif LN vardı. Oniki ayda, 16 hastada (%37,2) TR elde edildi ve tanı anında sistolik ve diyastolik kan basıncı ile eGFR'de anlamlı farklar vardı (sırasıyla, p=0,01, p=0,02 ve p=0,016). Proliferatif LN (p=0,024) ve interstisyel inflamasyonu olan hastalarda 12 aylık TR oranları daha düşük bulundu (p=0,04). Ayrıca, steroid ve siklofosfamid ile tedavi edilen PLN hastaları ile steroid ve mikofenolat mofetil (MMF) ile tedavi edilenler arasında 6 ve 12 aylık TR oranlarında anlamlı fark bulunmadı (p>0,05). Bununla birlikte, mikofenolat mofetil grubunda TR elde etme süresi daha kısaydı (p=0,048).

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Conclusion: LN remains a significant source of morbidity and mortality in patients with SLE; therefore, early diagnosis and prompt initiation of the treatment are crucial for renal and patient survival.

Keywords: Renal survival, lupus nephritis, end-stage renal disease, remission, induction therapy

Sonuç: LN, SLE hastalarında morbidite ve mortalitenin önemli bir kaynağı olmaya devam etmekte olup erken tanı ve tedavi böbrek ve hasta sağkalımı için kritik öneme sahiptir.

Anahtar Kelimeler: Böbrek sağkalımı, lupus nefriti, son dönem böbrek hastalığı, remisyon, indüksiyon tedavisi

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex, chronic, multisystemic autoimmune disease with a broad spectrum of clinical manifestations and severity (1). SLE manifests with a spectrum of clinical presentations, encompassing joint and cutaneous involvement, as well as potentially life-threatening renal, hematologic, and central nervous system manifestations. Recurrent disease flares and resulting organ damage contribute to elevated healthcare expenditures and diminished quality of life (2).

The pathogenesis of lupus nephritis (LN), the renal manifestation of SLE, involves the early formation and deposition of immune complexes containing autoantibodies in the kidneys, subsequently leading to inflammation, immune-mediated tissue damage, and fibrosis (3). The range of clinical presentations includes from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis. LN, which affects up to 50% of SLE patients, significantly contributes to morbidity and early mortality, serving as an indicator of a more severe form of SLE (4). Despite recent treatment advances, only 10-58% of patients with LN achieve a complete response (CR) in the first year of treatment, and approximately 20% of patients progress to end-stage renal disease (ESRD) within five years of diagnosis (5).

LN classification based on kidney biopsy findings has shown that more than 50% of patients have class III or IV LN. Histopathological indicators determining prognosis include the presence of crescents exceeding 50%, a high chronicity index, and tubulointerstitial disease (6). The clinical factors that were associated with poor prognosis were male sex, SLE duration, and African-American ethnicity (7). In addition, elevated serum creatinine, the presence and higher titre of anti-dsDNA, high antiphospholipid antibody, and persistent hypocomplementemia influence disease prognosis (8, 9). Therefore, prompt initiation of therapy is essential in LN, as delayed treatment is related to poor prognosis and increased risk of ESRD.

In LN, complete or partial renal response should be achieved for renal survival. The current guidelines define CR in LN as inactive urine sediment, normalisation of serum creatinine levels, and uPCR of less than 500 mg (10). Renal response should be achieved within six months or, at the latest, within 12 months after the initiation of treatment (11). The primary objective of this study was to conduct a comprehensive analysis of the clinical and histological characteristics of patients diagnosed with LN based on the kidney biopsy findings obtained at our institution. In addition, our study evaluated disease remission rates and identify the key factors influencing its achievement.

MATERIALS AND METHODS

Study population

A total of 128 patients diagnosed with SLE and followed up at our hospital between January 2012 and January 2021 were identified. Of these, 47 patients (36.7%) were diagnosed with LN based on kidney biopsy findings. Patients under the age of 18, those with a follow-up period of less than six months, and those with connective tissue disorders other than SLE were excluded from the study (n=3). Consequently, the study included 44 patients diagnosed with LN. All patients with LN are routinely prescribed hydroxychloroquine and an ACE inhibitor or ARB unless there is a contraindication. The institutional review board has approved the study's design and procedures according to the principles outlined in the Declaration of Helsinki and ethical standards for human experimentation (Date: 04.10.2021, 121/07). As the study was retrospective and all procedures performed were part of routine care, no informed consent was required.

Data collection

The patient's demographic, clinical, and laboratory data at diagnosis were retrospectively reviewed. Parameters such as sex, age at diagnosis, accompanying comorbidities, and body mass index were analysed. In addition, the biochemical parameters of the patients at the time of diagnosis, such as ALT, albumin, hemoglobin, white blood cell count, platelet count, estimated glomerular filtration rate (eGFR), urea, creatinine, sedimentation rate, serum complement level, presence of anti-dsDNA positivity, 24-h urine proteinuria levels and presence of active urine sediments like hematuria or leukocyturia were analysed. LN classification was made by evaluating the pathological data of the patients' kidney biopsies according to the ISN/RPS histopathological classification (12). The distribution for LN classes I-VI was determined by considering the dominant renal findings of the patients. In addition, the patients were grouped as non-proliferative and proliferative LN (PLN) according to the proliferative findings in the kidney biopsy.

Treatment and the renal response

Patients with LN were treated according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (13, 14). In patients with PLN, induction therapy was administered with intravenous methylprednisolone 250–500 mg/day (10-15 mg/kg/day) for three days, followed by oral prednisolone therapy starting at 1 mg/kg/day according to the ideal body weight and gradually decreasing the dose. In addition, during induction therapy, patients received mycophenolate mofetil (MMF) at a dose of 2-3 g per day (for six months) or intravenous pulse cyclophosphamide (CYC) 500 mg every two weeks (for three months) according to the EURO/Lupus protocol.

In the context of response assessment, CR is defined as a reduction in 24-h urine proteinuria or urine protein-creatinine (PCR) ratio to less than 0.5 g/g within 6-12 months after treatment initiation, accompanied by stabilisation or improvement in measured renal function (within ±10-15% of baseline). In cases where the level of proteinuria does not meet the criteria for CR, partial remission (PR) is characterised by a 24-h urine protein excretion reduction to below 3 g/day with at least a 50% decrease in proteinuria. The recently updated KDIGO LN guideline included primary effective renal response (PERR) in the definition of response assessment (14). PERR is characterised by PCR of less than 0.7 g/g, an estimated eGFR no more than 20% below baseline or at least 60 ml/min per 1.73 m^2, and the absence of any rescue therapy for treatment failure. The treatments received by the patients during their follow-up and treatment responses were also examined.

Statistical analysis

Continuous data in the study are presented according to distribution as mean±standard deviation or as median with the interquartile range. Categorical data, on the other hand, are shown as numbers and percentages. To compare the baseline characteristics between different groups, the researchers used the student t-test or non-parametric tests for continuous variables based on their distribution. For categorical variables, the chi-square test was employed. In this study, statistical significance was considered for p-values less than 0.05. Statistical analyses were conducted using the SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The study comprised 44 patients diagnosed with LN through renal biopsy. Among them, 32 (72.7%) were female, and the median follow-up period was 52.5 (6-117) months. At the time of diagnosis, the mean patient age was 36±10.8 years, with 12 (27.3%) patients having a history of hypertension. Notably, the serum albumin level at diagnosis was 3.0 (1.3-4.5) g/dL, and the 24-h urine proteinuria level was 4388 (594-16912) mg/day. Thirty-one (70.5%) of the patients diagnosed with LN had a known history of SLE, and the mean duration of diagnosis before biopsy was 25 months.

Because one patient died at the end of the 12-month follow-up period, the remission status was evaluated in 43 patients. At 12 months, 16 (37.2%) patients were in CR. Systolic and diastolic blood pressure values at the time of diagnosis were higher in patients who were not in CR at 12 months [131.4±12.2 vs. 120.4±12.1 mmHg (p=0.01) vs. 90.3±11.1 vs. 81.1±9.2 (p=0.02), respectively]. In addition, the eGFR level at the time of diagnosis was significantly lower in the patients who were not in CR at 12 months (p=0.02). The frequency of class II LN (43.8%) was higher in the patients who achieved CR (p=0.002), and the frequency of PLN (77.8%) was higher in the patients who did not achieve CR (p=0.024) at the end of the first year. Interstitial inflammation was also more prominent in the group that did not achieve CR (p=0.04). The patients' demographic, laboratory, and histological characteristics are shown in Table 1.

Among the eight patients diagnosed with class II LN, seven were treated with steroids, and one patient was followed with conservative management. Treatment regimens were varied in the cohort of patients with class V LN (n=8). Two patients were administered steroid monotherapy, four patients received a combination of steroids and MMF, and one patient was treated with steroids combined with CNI. While 6 (75%) of the patients with class II LN (n=8) achieved CR at six months, only one patient (12.5%) with class V LN (n=8) achieved CR. At 12 months, 7 (87.5%) patients with class II LN and 2 (25%) patients with class V LN were in CR (Figure 1). In 29 patients with PLN, the PR rate at 6 months was 69% (n=20), while the CR rate was 13.8% (n=4). At 12 months, 16 patients (57.1%) were in PR and 7 (25%) were in CR. Fourteen patients (48.3%) received steroid+CYC, and 15 (51.7%) received steroid + MMF combination for induction therapy. No difference was found between the two treatment groups regarding remission rates at 6 and 12 months. However, the median time to CR was shorter in the steroid+MMF group than in the steroid+CYC group [9 (0-27) months vs. 21.5 (0-74) months; p=0.048]. The induction treatments and response rates of the patients diagnosed with PLN are shown in Table 2.

The response status of the patients at their last follow-up was also evaluated. It was determined that 31 out of 44 patients (70.5%) were in CR, 7 (15.9%) were in PR, 4 (9.1%) were unresponsive to treatment, and 2 (4.5%) had died. The CR rate was 69% in patients with PLN and 73.3% in the non-proliferative patient group (Table 3). Moreover, we examined PERR, the latest renal response definition in patients with LN. PERR rates of the patients were found to be 46.5% at the 12 months and 72.7% at the last follow-up (Figure 2).

Table 1: Clinical, laboratory and histological findings of patients with Lupus nephritis

	Total (n=44)	Non-complete remission n=27 (62.8%)	Complete remission in the first year n=16 (37.2%)	P value
Demographic data				
Age (years)	36.0±10.8	37.5±10.6	34.1±11.1	0.32
Female, n (%)	32 (72.7)	21 (77.8)	10 (62.5)	0.31
Previous SLE diagnosis, n (%)	31 (70.5)	20 (74.1)	9 (56.2)	0.23
HT, n (%)	12 (27.3)	20 (74.1)	9 (56.2)	0.23
BMI (kg/m²)	20-34.2	26.2 (21.5-34.2)	24.6 (20-34.2)	0.13
Systolic BP (mmHg)	127.3±13.1	131.4±12.2	120.4±12.1	***0.01***
Diastolic BP (mmHg)	87.2±10.3	90.3±11.1	81.1±9.2	***0.02***
LN follow-up time (months)	52.5 (6-117)	57 (22-103)	47.5 (18-117)	0.60
Laboratory data				
WBC count (/µL)	6.9 (1.4-13.9)	6.8 (2.7-12.5)	7.5 (1.4-13.9)	0.20
Hemoglobin (g/dL)	11.2 (4.7-15.8)	11.1 (6.5-15.8)	11.7 (6.7-15.5)	0.48
Platelet count (×1000/µL)	244 (63-779)	243 (63-779)	255 (116-549)	0.13
ALT (U/L)	14.5 (3-50)	13 (3-43)	14.5 (7-50)	0.44
Serum creatinine (mg/dL)	0.8 (0.4-3.2)	1.2 (0.4-3.2)	0.8 (0.4-2.8)	0.08
eGFR (ml/min/1.73 m²)	89 (16-137)	75 (16-134)	116 (28-137)	***0.02***
Serum albumin (g/dL)	3.0 (1.3-4.5)	3.0 (1.3-4.5)	2.8 (1.5-4.5)	0.75
ESR (mm/h)	34.5 (4-123)	32 (4-123)	46 (11-93)	0.24
Low serum C3, n (%)	25 (56.8)	14 (51.9)	10 (62.5)	0.50
Low serum C4, n (%)	21 (47.7)	12 (44.4)	8 (50)	0.72
Anti-ds DNA positive, n (%)	24 (54.5)	13 (48.1)	10 (62.5)	0.36
Presence of RBC/WBC in urine (n, %)	24 (54.5)	14 (51.9)	9 (56.2)	0.78
Proteinuria (mg/24 h)	4388 (594-16912)	4582 (1476-12622)	4308 (594-16912)	0.41
Nephrotic range proteinuria, n (%)	25 (56.8)	17 (62.9)	8 (50.0)	0.74
Class of LN, n (%)				
II	8 (18.2)	1 (3.7)	7 (43.8)	***0.002***
III	12 (27.3)	10 (37)	2 (12.5)	0.16
IV	16 (36.4)	10 (37)	5 (31.2)	0.70
V	8 (18.2)	6 (22.2)	2 (12.5)	0.69
Proliferative LN	29 (65.9)	21 (77.8)	7 (43.8)	***0.02***
Histologic features				
Endocapillary proliferation, n (%)	26 (59.1)	18 (66.7)	7 (43.8)	0.14
Fibrinoid necrosis, n (%)	7 (15.9)	3 (11.1)	3 (18.8)	0.66
Hyaline wire loops (n, %)	27 (61.4)	19 (70.4)	7 (43.8)	0.08
Fibrocellular crescents, n (%)	15 (34.1)	10 (37)	4 (25)	0.42
Glomerulosclerosis, n (%)	32 (72.7)	22 (81.5)	9 (56.2)	0.09
Interstitial inflammation, n (%)	33 (75)	23 (85.2)	9 (56.2)	***0.04***
Interstitial fibrosis, n (%)	24 (54.5)	17 (63)	6 (37.5)	0.11
Tubular atrophy, n (%)	30 (68.2)	18 (66.7)	11 (68.8)	0.89

BMI: Body-mass index, BP: Blood pressure, CR: Complete remission, eGFR: estimated glomerular filtration rate, ESR: Erythrocyte sedimentation rate, HT: Hypertension, LN: Lupus nephritis, RBC: Red blood cell, SLE: Systemic Lupus erythematosus, WBC: White blood cell

In addition, the maintenance treatment regimens were reviewed. Thirty-two patients received maintenance therapy after remission. Of these, 26 (81.3%) were treated with MMF at a median dose of 1500 mg/day for an average of 39.2±25.8 months, while 6 (18.7%) received AZA at a median dose of 100 mg/day for 35.6±8.7 months (Table 4). We identified eight patients who experienced flares in the long-term follow-up. All patients with flare history had class III/IV LN. 6 of those patients were treated with CYC, and 2 of them with MMF for renal flares of LN.

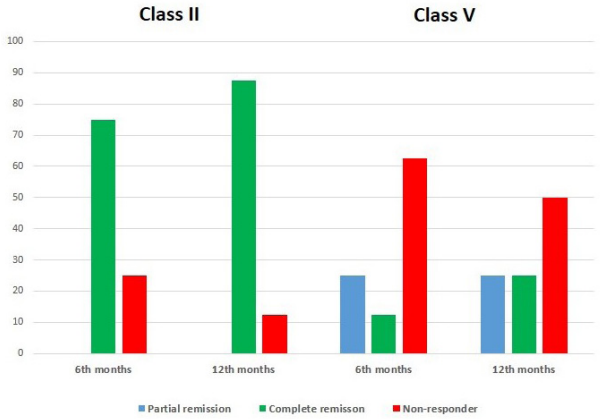

Figure 1: Partial and complete remission rates in class II and class V patients

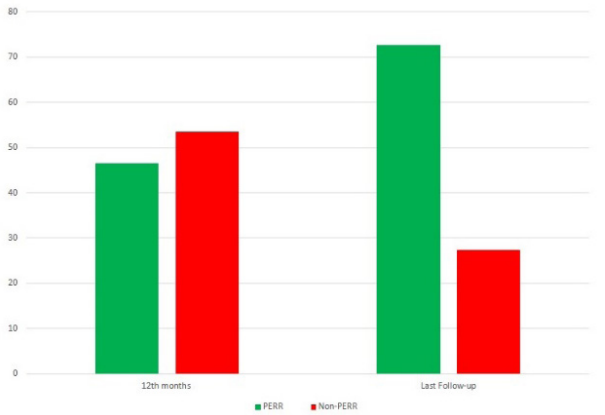

Figure 2: Primary efficacy renal response of patients with lupus nephritis

Table 2: Remission status of patients with proliferative lupus nephritis according to induction therapy

	Total n=29	Steroid+CYC n=14 (48.3 %)	Steroid+MMF n=15 (51.7%)	P value
6th months				
Partial remission, n (%)	20 (69)	9 (64.3)	11 (73.3)	0.70
Complete remission, n (%)	4 (13.8)	1 (7.1)	3 (20)	0.60
Non-responder, n (%)	5 (17.2)	4 (28.6)	1 (6.7)	0.17
12th months				
Partial remission, n (%)	16 (57.1)	9 (69.2)	7 (46.7)	0.23
Complete remission, n (%)	7 (25)	2 (15.4)	5 (33.3)	0.39
Non-responder, n (%)	5 (17.9)	2 (15.4)	3 (20)	0.57
Median time to partial remission (months)	5 (0-28)	5 (0-28)	4 (0-24)	0.47
Median time to complete remission (months)	10 (0-74)	21.5 (0-74)	9 (0-27)	***0.048***

CYC: Cyclophosphamide, MMF: Mycophenolate mofetil

Table 3: Treatment response of patients with lupus nephritis at the last follow-up

	All patients n=44	Non-proliferative LN patients n=15 (34.1%)	Proliferative LN patients n=29 (65.9%)
Partial remission, n (%)	7 (15.9)	1 (6.7)	6 (20.7)
Complete remission, n (%)	31 (70.5)	11 (73.3)	20 (69)
Non-responder, n (%)	4 (9.1)	2 (13.3)	2 (6.9)
Death, n (%)	2 (4.5)	1 (6.7)	1 (3.4)

Table 4: Maintenance treatment regimens of patients with lupus nephritis

Treatment	Total Patients (n=32)	Dosage (mg/d)	Duration (months)
MMF, n (%)	26 (81.3)	1500 (1000-2000)	39.2±25.8
AZA, n (%)	6 (18.7)	100 (100-150)	35.6±8.7

AZA: Azathioprine, MMF: Mycophenolate mofetil

DISCUSSION

This study examined patients' general characteristics and remission status followed up with LN. It was found that patients who achieved CR at 12 months had better initial eGFR and lower systolic and diastolic BP. While the frequency of class II LN was higher in the patient group that achieved CR, the frequency of PLN was higher in patients that did not achieve CR. In addition, it was seen that there was no difference in the remission rates between the induction treatment regimens in patients with PLN at 6 and 12 months. However, the median time to achieve CR was shorter in the patients with PLN receiving steroids + MMF as an induction therapy.

LN is the most common and essential visceral complication of SLE and is the leading cause of death in patients with SLE (15). Treatment response is critical in LN, and it has been shown that achieving a CR is related to the prognosis and progression to ESRD (16, 17). Studies have shown that CR rates in patients with LN vary between 10% and 40% (18). This study found that the CR rate was 37.2% at 12 months. Although the CR rates were low in the first year of our study, it should be noted that some of our patients achieved PR in the first year. Our higher CR rate (70.5%) in the long-term follow-up may be related to the fact that some patients with PR achieved CR after the first year of follow-up. In a study conducted by Gatto et al, the median time to achieve sustained clinical response was found to be 1.44 years (0.69–3.58), supporting the observation that CR in LN patients may occur even after more than one year (19).

Besides, systolic and diastolic blood pressures measured at diagnosis were higher in patients who did not achieve CR. Some studies have shown that hypertensive LN patients are associated with worse renal prognosis and mortality (20, 21). Although our results show that the frequency of HT is similar between the groups, high systolic and diastolic BPs may still influence remission. Similar to our study, a study from South Africa showed that high systolic and diastolic BPs in patients with PLN are associated with ESRD and death (22).

In addition, it was observed that patients who did not attain CR exhibited lower eGFR levels at the time of diagnosis than those who achieved remission. Similar to our study, Pirson et al. showed that patients in remission during follow-up had better baseline eGFR levels (23). This condition may be related to the more severe LN involvement in patients with low initial eGFR. In support of this finding, patients who did not achieve CR at the end of the first year had higher rates of proliferative LN and interstitial inflammation in their histopathological examinations. Many studies have shown that PLN is associated with lower CR rates and worse renal survival (24-26). Similar to our study, Lee et al. demonstrated that detecting higher interstitial inflammation in kidney biopsy increased the risk of ESRD and CKD in patients (Hazard ratio 4.67 and 3.8, respectively) (27). We also found that class II LN was more common in patients who achieved CR. Class II LN is considered a mild form of LN with a better prognosis and higher CR rates (28).

The guidelines recommend steroid therapy in combination with immunosuppressive therapy for patients with active class III/IV±V LN (13, 14, 29). In treating LN, a standard protocol involves an initial phase of intense immunosuppression lasting 3 to 6 months, followed by a long-term maintenance phase with less intensive immunosuppression to prevent renal flare. This comprehensive approach is designed to effectively manage the condition and mitigate the risk of disease recurrence. In this investigation, we assessed the remission rates at 6 and 12 months based on the induction regimen in patients with PLN. The remission rates at both 6 and 12 months were comparable between the groups that received steroid + CYC and those that received steroid + MMF. In randomised controlled trials comparing the efficacy of these two regimens, the induction remission rates were similar in both groups (30-32). Besides, the time required to achieve CR was similar between these treatments (32, 33). However, our study found that 69% of patients diagnosed with PLN achieved CR in the long-term follow-up, and the patients who received steroid + MMF treatment had a shorter median time for CR.

The study's limitations should be noted, given its single-centre, retrospective design, which could limit the generalizability of the results. Second, the study's reliance on a localised population and its relatively small sample size may constrain the broader applicability of the findings. In addition, the absence of SLE activity indices, such as SLEDAI or BILAG, has prevented us from comprehensively addressing the extrarenal manifestations of lupus. Finally, some missing parts in the biopsy data limited our analysis of the activity and chronicity indices. These limitations should be carefully considered when interpreting the study's outcomes and implications.

CONCLUSION

In conclusion, despite advances in LN treatment, CR rates are still low in the first year of treatment. Although the CR rates of induction treatments applied to patients with PLN are comparable in the first year, the median time to achieve CR is shorter in patients receiving steroids and MMF. Our results need to be supported by prospective and multicenter studies. New treatment regimens with more effective and fewer side effects must increase the success rate of LN treatment.

Ethics Committee Approval: Ethics committee approval was

received for this study from the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 04.10.2021, No: 121/07).

Informed Consent: As the study was retrospective and all procedures performed were part of routine care, no informed consent was required.

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Conflict of Interest: The authors have no conflict of interest to declare.

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