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Treatment Results of Patients With Lupus Nephritis: A Single Center's Experience

Lupus Nefritli Hastalarda Tedavi Sonuçlarının Değerlendirilmesi: Tek Merkezli Deneyim

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Abstract

Objective: Lupus nephritis (LN) is a type of organ involvement of systemic lupus erythematosus (SLE) that leads to disease-related morbidity and mortality. Lack of good treatments for LN continues to be problematic. Many different treatment protocols are applied in treatment centers. Not every treatment protocol is successful. Moreover, patients who reached remission may present with exacerbations. In this study, we aimed to evaluate the treatment results of our patients and investigate their remission rates as well as factors that affect remissions.

Materials and Methods: We retrospectively investigated the results of 41 patients who were diagnosed with lupus nephritis after kidney biopsy in the Nephrology and Immunology-Rheumatology departments of Atatürk University Medical Faculty Training Hospital between January 2000 and December 2008. Demographic information, clinical history and laboratory results were collected from each patient's records. The relationships among clinical, laboratory, demographic parameters and remissions were investigated. The patients were grouped in terms of urine protein levels; patients with urine protein < 330 mg/day were regarded as in remission and patients with urine protein ≥ 330 mg/day were were regarded as uncontrolled.

Results: At the end of a 12-month period of therapy, 24 (58.5 %) of the patients were in remission. There were no statistically significant relationships among age, sex, anti-ds-DNA, C3, C4, activity indexes, chronicity indexes, serum level of creatinine, urine protein levels and remission ($p>0.05$). We compared class 3 LN patients at the 6th and 12th months according to treatment protocols. Azathioprin or mycophenolate mophetil were significantly better at placing urine protein levels in remission as compared to cyclophosphamide ($p<0.05$).

Conclusion: According to our study, no relationship was found between basal clinical and laboratory parameters and patient remission. Response rates of our LN patients were similar to those in the literature. However, complete remission is still a problem in LN. The results of the protocols used in the treatment of LN show similarities. Although there are some data suggesting that MMF used in recent years is effective, it should be supported by prospective multicenter studies. It is important to note that it is difficult to achieve complete remission in LN patients.

Key Words: Lupus nephritis, Treatment, Remission

Özet

Amaç: Lupus nefriti (LN), Sistemik lupus eritematozisin mortalite ve morbiditesine neden olan organ tutulumlarındandır. LN tedavisi, önemli bir problem olmaya devam etmektedir. Merkezler farklı tedavi protokolleri uygulamaktadır. Hiçbir protokol kesin tedavi sağlamadığı gibi, remisyondaki bir hastada daha sonra hastalık alevlenmesi gözlenebilmektedir. Bu çalışmada, merkezimizde takip ettiğimiz hastaların tedavi sonuçlarını değerlendirmeyi, remisyon oranlarımızı ve remisyona etki eden faktörleri araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmamızda, Ocak 2000-Aralık 2008 tarihleri arasında Atatürk Üniversitesi Tıp Fakültesi Nefroloji ve Romatoloji-İmmünoloji kliniklerinde böbrek biyopsisi sonucu LN tanısı konularak tedavi başlanan 41 hastanın tedavi sonuçları retrospektif olarak değerlendirildi. Hastalara ait bilgilere hasta dosyalarından ulaşıldı. Hastaların klinik, laboratuar ve demografik özelliklerinin remisyonla ilişkisi araştırıldı. Proteinürisi 330 mg/gün altında olan hastalar remisyona girmiş grup olarak, 330 mg/gün'ün üstünde olan hastalar da remisyona girmemiş grup olarak gruplandırıldı.

Bulgular: Bir yıllık tedavi sonrasında hastaların 24'ü (%58.5) tam remisyona girdi. Yaş, cinsiyet, Anti ds-DNA, Kompleman 3 ve 4, aktivite ve kronisite indeksleri, serum kreatinin ve proteinüri düzeyleri ile remisyon arasında bir ilişki bulunamadı ($p>0.05$). Klas 3 LN olan hastaların idame tedavisinde kullanılan azatioprin veya mikofenolat mofetil (AZA/MMF) ile siklofosfamid (CyP)'in 6. ve 12. aydaki proteinüri düzeyleri karşılaştırıldığında, AZA/MMF alan grupta proteinüri düzeyleri CyP grubuna göre anlamlı düzeyde azalmaktaydı ($p=0.04$).

Sonuç: Sonuç olarak, çalışmamızda hastaların bazal klinik ve laboratuar parametreleri ile remisyon arasında bir ilişki bulunamamıştır. Lupus nefritli hastalarda uygulamış olduğumuz tedavi rejimlerine alınan sonuçlar literatürdeki verilerle benzerlik göstermektedir. Bununla birlikte LN'de tam remisyon hala sorun olmaya devam etmektedir. LN'nin tedavisinde kullanılan protokollerin sonuçları birbirine benzerlik göstermektedir. Son yıllarda kullanılmakta olan MMF'in etkili olduğuna dair veriler olsa dahi, prospektif çok merkezli çalışmalarla desteklenmelidir. Daha etkili ve yan etkisi daha az olan yeni tedavi rejimlerine ihtiyaç vardır.

Anahtar Kelimeler: Lupus nefriti, Tedavi, Remisyon

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Introduction

Systemic Lupus Erythematosus (SLE) is a systemic, chronic, autoimmune disease in which pathogenic auto-antibodies and immune complexes cause tissue lesions in many target organs. It has a wide clinical spectrum, ranging from very mild forms to severe systemic involvement that progresses to involve major organs and may cause significant morbidity and mortality. Its clinical progression and prognosis are variable and can involve multiple exacerbations and remissions. Genetic, hormonal, immunological and environmental factors together play a role in its pathophysiology [1]. Lupus nephritis (LN) is the major cause of morbidity and mortality in SLE. Approximately 66% of SLE patients experience kidney involvement. Up to 50% of patients have urinary abnormalities at diagnosis, and up to 75% are ultimately affected over the course of the disease [2].

Despite all of the studies that have been done and the use of new drugs, the treatment of LN is still a significant challenge. The the treatment standard for patients suffering from lupus nephritis is still debated. Although there are new studies in which different treatment protocols are carried out according to the different histopathological forms defined by the World Health Organization (WHO), symptoms are variable according to scientists. We should remember that early treatment of LN patients can inhibit the progression of renal insufficiency and increase survival [3]. In this study, we aimed to evaluate the treatment results of LN patients in our center and ascertain our remission rates and factors related to remission.

Materials and Methods

In our study, we retrospectively evaluated the treatment results of 41 patients who were diagnosed with lupus nephritis from a renal biopsy at Atatürk University Faculty of Medicine, Nephrology and Rheumatology-Immunology clinics between January 2000 and December 2008. Demographic, laboratory and clinical data were collected from patient files.

In our study, the relationships among the clinical, laboratory and demographic features of LN patients and remission were studied. The patients with urine protein under 330 mg/day were grouped as remitted, and those with urine protein over 330 mg/day were grouped as unremitted.

Features of the patient

The data regarding sex and age of the patients were collected from the patient files (Table 1). The presence of 4 out of 11 diagnostic criteria issued by the American Rheumatology Society was used to diagnose our patients with SLE [4].

Laboratory parameters

Urine protein levels of the patients were measured by Atatürk University, Biochemistry Department Laboratory.

Table 1. Comparison between remitted and unremitted group

	Remitted (n=24)	Unremitted (n=17)	P
Age (years)	33.1±9.7	25.8±3.8	0.61
Gender (male/female)	3/21	1/16	0.482
Anti ds-DNA (+)	15	10	0.812
Complement 3 (mg/dL)	76.3±38.3	46.5±36.6	0.07
Complement 4 (mg/dL)	12.9±11.4	11.3±11.2	0.73
Basal PU (g/day)	4.2±3.3	4.0±2.3	0.87
Basal SCr (mg/dL)	1.2±0.6	2.1±1.7	0.17
Activity index	7.06±2.92	6.29±3.7	0.546
Chronicity index	3.85±2.68	4.57±1.9	0.507

(PU) proteinuria; (SCr) serum creatinine

Total protein measured from spot urine obtained in the first sample of the morning was measured by turbidimetry after denaturing with benzathonium chloride. The amount of urine creatinine was measured with Jaffe colorimetry. Protein level (g/day) was determined by calculating microprotein creatinine (mg/dL) rates in spot urines of all patients.

Complement 3 (C3) and complement 4 (C4) rates of the patients were studied with nephelometry. ANA and anti-ds DNA levels were examined with indirect fluorescence. Serum creatinine levels were examined with spectrophotometry.

Histopathological evaluation

Renal biopsy was carried out in patients diagnosed with SLE and who were believed to have lupus nephritis. In 2003, histopathological typing was staged like the type given in Table 2 by ISN/RPS [1].

Treatment protocols

Methylprednisolone (MP), cyclophosphamide (CyP), azathioprine (AZA), and mycophenolate mofetil (MMF) were given for the treatment of LN according to the following protocol that takes histopathological categories into consideration [1].

Class 2 LN patients were given MP as immunosuppressive therapy. Class 3 LN patients were given MP+CyP for the first 6 months and were then involved in two different treatment protocols as maintenance treatment in the second 6 months.. While some patients were given MP+CyP treatment, others were given MP+AZA or MMF. All patients in the Class 4 group were given MP+CyP. Class 5 patients were given MP+CyP. Class 6 patients were not given immunosuppressive therapy, but rather palliative therapy.

After being given as 1 mg/kg daily for two weeks, MP dosage was continued at 0.2 mg/kg/day as maintenance dosage by reducing the present dosage to 5 mg in a week. AZA was started at 1 mg/kg daily and was gradually increased to a 2-3

Table 2. Comparison maintenance treatment between AZA/MMF and CyP in class 3 lupus nephritis

	Urine Protein			Serum Cr		
	6th month	12th month	p	6th month	12th month	p
AZA/MMF (n=7)	0.75±0.69	0.44±0.47	0.043	0.88±0.53	0.77±0.32	0.25
CyP (n=8)	1.8±2.3	1.35±2	0.069	1.32±0.32	1.23±0.96	0.21
(AZA/MMF) azathioprine or mikofenolate mofetil; (CyP) cyclophosphamide						

Table 3. Biopsy results and remission rates

Class	Remitted (n=24)	Unremitted (n=17)	Total (n=41)
2	7	3	10
3	10	5	15
4	5	6	11
5	2	0	2
6	0	3	3

mg/kg/day dosage. MMF was given as a 1-2 g/day dosage. Cyclophosphamide at 10 mg/kg was given intravenously every month for 6 months. After that, it was given once every two months using the same dosage.

Complete remission in LN patients was considered to be a decrease in microprotein/creatinine ratio in spot urine to under 330mg/day [5].

Statistical analysis

The data was given as numerical percentages, averages and standard deviations. Statistical analysis was performed using SPSS 11.5. Response to treatment and complete remission rates were given as a percentage. To determine the relationship between the factors affecting complete remission, chi-square testing of categorical variables was used. The relationship between the activity and chronicity indices of our patients and remission was analyzed with t-tests of independent samplings. The effects of two different treatment protocols given after the 6th month in class 3 LN patients with proteinuria and elevated serum creatinine were compared with the Mann Whitney U test. The level of significance was accepted as $p<0.05$.

Results

The files of 41 patients whose treatments were started after being diagnosed with lupus nephritis between January 2000 and December 2008 were examined retrospectively. Demographic and laboratory data of the patients is given in Table 1.

Thirty-seven (90.8%) LN diagnosed patients were women, and four (9.2%) were men. Average age of the patients was determined to be 31.9±9.4 years (18-54 years). No relationship was found between the age or sex of the patients and remission ($p>0.05$) (Table 1).

While ANA was determined to be positive in 41 (100%) patients, anti-dsDNA was found to be positive in 25 (60.9%) patients and negative in 16 (39.1%) patients. No relationship was found between anti-dsDNA positivity and remission ($p>0.05$) (Table 1). Serum C3 and C4 were found at low levels in 31 (75.4%) patients. In those who were unremitted, C3 and C4 levels were lower, but this difference was not statistically significant ($p>0.05$) (Table 1).

Twenty patients (48.8%) had urine protein levels in the nephrotic range before treatment. No relationship was found between basal protein levels of the patients and remission ($p>0.05$) (Table 1). Nineteen patients (46.3%) had plasma creatinine levels that were 1.3 mg/dl or higher before treatment. No relationship was found between basal serum creatinine levels of the patients and remission ($p>0.05$) (Table 1).

According to the WHO histopathological staging of the patients, class 3 LN was most frequently determined. The visibility rates of the stages are given in Table 1. No relationship was found between the activity/chronicity indices and remission ($p>0.05$) (Table 1).

Complete remission was achieved in 24 (58.5%) LN patients who were treated for over a year. In Table 3, the treatments given in accordance with the stages and remission rates are given.

The results of AZA/MMF and CyP used in maintenance treatment of the LN class 3 group were compared. The decrease in urine protein in the group taking AZA/MMF was found to be statistically significant ($p=0.043$) (Table 2). When serum creatinine levels were examined, no statistically significant difference was found between the creatinine levels in the 6th and 12th months ($p>0.05$) (Table 2).

In conclusion, despite new studies and new drugs, the treatment of LN is still a significant problem. Different centers continue to use different treatment protocols. Lupus nephritis may convert from one form to another over time. No treatment is definitive. Patients may undergo remission even after months of disease exacerbation. It is known that unintended adverse effects of the treatment may cause significant problems that are as serious as the disease itself (e.g., infertility, neutropenia). All of these facts make treatment standardization difficult [4, 6].

It is known that LN is mostly seen in teenagers and women. Similar to our study, Austin et al. [7] found that age and sex did not affect disease remission.

Al Arfaj et al. [8] found that out of 299 LN patients 99.3% were ANA positive, while 81.6% were anti-dsDNA Ab positive. In our study, positive ANA and anti-dsDNA was found in 100% and 60.9% of our patients, respectively. No relationship was found between anti-dsDNA and remission in LN patients in Austin et al. [7]. Similarly in our study, no anti-dsDNA positivity or a correlation between titer and remission was found.

The remissions in C3 and C4 levels are one of the important indicators in diagnosing lupus nephritis. A decrease in complement levels was found in 60-84% of patients in some studies [9]. Serum C3 and C4 levels were found to be low in 75.6% of our patients. These results show similarities with the data in the literature [10,11]. Austin III et al. [7] found that C3 levels in unremitted patients were lower than those who were in remission. In our study, C3 levels of unremitted patients were found to be relatively lower than those in remission. However, this difference was only borderline significant (p=0.07). We believe that larger scale studies are needed to draw more specific conclusions. Proteinuria rates in nephrotic level in LN were reported as 26-48.5% [10-12]. In our study, nephrotic level urine protein was found in 42.9% of the patients. Additionally, no relationship was found between basal protein level and remission.

The rate of the LN patients whose serum creatinine level was determined 1.3 g/dl and over it was reported between 8% and 28.5% [10, 11]. Al Arfaj et al. [8] found that 65.9% of patients had creatinine clearance under 75 ml/min. Serum creatinine level was found to be 1.3 g/dl or higher in 46.3% of our patients. In our study, no relationship was found between basal serum creatinine and remission.

In the cases where the activity index is under 12, lesions turn back with an effective treatment, and, in cases where it is over 12, renal insufficiency risk increases. It is reported that the chronicity index increases the renal insufficiency risk if it is 4 or higher. All of the chronicity index symptoms are important, but the most important is tubular atrophy [13, 14]. Austin III et al. [7] grouped the activity or chronicity indices as low or high but could not find a relationship between activity chronicity indices and remission.

In our study, there were no patients diagnosed as Class 1 lupus nephritis. There were 10 patients diagnosed as Class 2 lupus nephritis. After being given 1 mg/kg daily for two weeks, MP dosage was continued 0.2 mg/kg/day as maintenance dosage by reducing the present dosage 5 mg in a week. Complete remission was seen in 7 (70%) of the patients after treatment and a 50% decrease in urine protein was seen in 3 (30%) of the patients. Al Arfaj et al. [8] found that after treatment, 90.7% of class 2 patients went into remission. They correlated this with early diagnosis and treatment.

In Contreras et al. [15], a group was given Cyp+MP and another group was given AZA+MP maintenance treatment. In the 72nd month of treatment, the rate of development of renal insufficiency in the AZA+MP group was found to be higher than in the CyP+MP group. However, taking into consideration the adverse effects of CyP, they stated that AZA may be preferred in the maintenance treatment of patients in the propagation period. In another study by Nossent et al. [16], AZA and CyP were compared in patients with proliferative LN. It was observed that 58% of patients given AZA+MP and 65% of patients given CyP enjoyed a 5-10 year remission rate. Flanc et al. [17] showed that in patients diagnosed with diffuse proliferative lupus nephritis, remission rates of patients given CyP+MP were higher than the remission rates of patients given AZA+MP.

Briggs et al. [18] stated that urine protein successfully decreased after using MMF in two patients diagnosed with proliferative lupus nephritis. Hu et al. [19] gave MMF to 23 diffuse proliferative lupus nephritis patients and conventional high dose cyclophosphamide treatment to another 23 patients. After treating for 6 months, 50% decrease in proteinuria in MMF group was found significantly more than the cyclophosphamide. In our study, Class 3 and Class 4 LN diagnosed patients were evaluated within different groups. Fifteen patients who were Class 3 LN were carried out using the MP+CyP protocol in the first six months. After the 6th month, two treatment protocols were carried out as maintenance treatment; while 7 (46.7%) of them were given MP+AZA/MMF combination, 8(53.3%) of them were given MP+CyP. When proteinuria and serum creatinine levels in the sixth and twelfth months of these two treatment protocols were compared, the urine protein was lower in the AZA/MMF group than in the CyP group. There was no difference in serum creatinine levels between the two groups. In our study, 11 patients diagnosed as Class 4 LN underwent first line treatment. Maintenance treatment was given as a MP+CyP combination. Five (45.5%) patients underwent complete remission after treatment.

Moc et al. [20] gave low dose MP+AZA to 38 membranous LN patients. At the end of a year, taking urine protein levels into consideration, 24 patients (67%) underwent complete remission, 8 patients (22%) underwent partial remission and 4 patients (11%) experienced persistent proteinuria. They suggested that this treatment is most suitable in the initial stage of membranous lupus nephritis. Spetie et al. [21] gave ACEI and statin in addition to MP and MMF in 13 membranous LN patients. After 6 months, they encountered complete and partial remission in 10 out of 13 (76.9%) patients. After 16 months, they achieved complete remission in 11 (84.6%) patients. In our own clinic, complete remission was obtained in both patients with Class 5 lupus nephritis by giving MP+CyP. Our remission rate was 100%. However, it should be noted that our sample size was small.

According to our study, no relationship was found between basal clinical and laboratory parameters and patient remission. The results we obtained from our LN treatments were similar to those in the literature. However, complete

remission is still a problem in LN. The results of the protocols used in the treatment of LN show similarities. Although there are some data suggesting that MMF used in recent years is effective, it should be supported by prospective multicenter studies. New treatment regimens that are more effective and have fewer adverse effects are needed.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

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