LONG-TERM OUTCOME OF PATIENTS WITH LUPUS NEPHRITIS: A SINGLE CENTER EXPERIENCE

Senija Rašić[1]*, Amira Srna[1], Snežana Unčanin[1], Jasminka Džemidžić[1], Damir Rebić[1], Alma Muslimović[1], Maida Rakanović-Todić[2], Aida Hamzić-Mehmedbašić[1]

[1] Clinic for Nephrology, University of Sarajevo Clinics Centre, Bolnička 25, 71 000 Sarajevo, Bosnia and Herzegovina

[2] Institute for Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Sarajevo, Čekaluša 90, 71 000 Sarajevo, Bosnia and Herzegovina

* Corresponding author

Abstract

Lupus nephritis (LN) is an immune inflammation of kidneys caused by systemic lupus erythematosus (SLE), a chronic inflammatory disease that affects the body's immune system. Aim of this study was to analyze clinical manifestation and treatment results of patients with LN. Forty one patients with clinical signs of LN were included in the study. Mean age of patients was 31,9±12,1 years in the moment of first diagnosis of LN, with female-male ratio 8:1. Renal disease was pathohistologically (PTH) verified in 53,7% of patients (4 pts with class III, 17 pts with class IV, one pt with class V of lupus nephrites). Patients with high nephrotic proteinuria were treated with pulse dose of methylprednisolone and pulse doses of cyclophosphamide (CYC) in induction therapy. Corticosteroid and CYC were continued according to treatment protocol. The other group of LN patients with lower nephrotic proteinuria was treated with mycophenolate mofetil (MMF) in induction therapy at a dose of 2x1 g/day for six months, and than in maintenance 2x0,5 g/day. The patients with non-nephrotic proteinuria and normal renal function were treated with oral prednisolone 0,75-1 mg/kg/day in a single morning dose, and then gradually reduced to the dose of maintenance. The mean time of patient's follow-up was 10,9±4,1 years. Partial renal remission was accomplished in 29,2% pts, and complete remission in 60,9% pts for period of 17,2±13,3 months from the beginning of the treatment. Duration of complete renal remission was 30,1±19,1 months. During the period of follow-up, 29,3% pts developed at least one nephritic flare and were treated again. These results confirmed that the aggressive form of lupus nephritis should be treated associating cyclophosphamide with corticosteroids therapeutical regiment. MMF is a new promising immunosuppressive drug for a treatment of this serious disease.

KEY WORDS: lupus nephritis, cyclophosphamide, mycophenolate mofetil, treatment outcome

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease, which affects kidney in up to 60% of patients with SLE (1). Renal injury is the main cause of mortality and morbidity of patients with SLE (2). Lupus nephritis (LN) may be presented from mild asymptomatic proteinuria to rapidly progressive glomerulonephritis with haematuria and red cell casts. Some patients develop acute renal failure, or some degree of chronic kidney disease. Nephrotic syndrome (NS) is present in 45-65% of cases. The diagnosis of lupus nephritis is based not only on clinical features alone, than also on renal biopsy, which determines histopathological findings in six classes of lesions.

The treatment of lupus nephritis is focused on reducing disease progression, achievement of complete renal remission and improved long-term outcome of kidney disease. There is general agreement that diffuse or focal proliferative lupus nephritis (class III, IV) is associated with poor renal prognosis and generally requires aggressive therapy. Aim of this study was to analyze clinical manifestations and treatment results of patients with LN.

Materials and Method

Patients with more severe histopathological findings and nephrotic syndrome (30 patients) with proteinuria more than 5 g/day received an induction therapy of methylprednisolone pulse dose of 500-1000 mg/day for three consecutive days with pulse doses of cyclophosphamide (CyC) of 0,5 g per square meter of body-surface area. Dose of corticosteroid was reduced on 0,5-1 mg/kg/day by oral prednisolone for 1-2 months and than gradually reduced to the minimum effective dose for maintenance, while pulse doses of CyC were continued according to the treatment protocol. The other group of LN patients (7 patients) with nephritic proteinuria between 3,5-5 g/day was treated with mycophenolate mofetil (MMF) in induction therapy on a dose of 2x1 g/day for 6 months, and than reduced to the maintenance of 2x0,5 g/day. All patients (pts) received oral prednisolone 0,75-1 mg/kg/day for 1-2 months, with gradually tapering to the minimum effective dose. The patients with non-nephrotic proteinuria (between 0,25 and 3,5 g/day) and normal renal function (4 pts) were treated with oral prednisolone 1 mg/kg/day in a single morning dose 1-2 months and then gradually reduced to the dose of maintenance. All the patients were followed up for 10,9± 4,1 years. An induction therapy was started again in any case of flares of activity (3).

We defined clinical features of LN as:

- nephrotic syndrome: proteinuria >3,5 g/day with plasma albumin < 30 g/l
- non-nephrotic proteinuria: proteinuria between 0,25 and 3,5 g/day
- acute renal insufficiency (ARI): increased in serum creatinine an least ≥1,5 time of baseline (last) value or decreased glomerular filtration rate (GFR) ≥25% according RIFLE criteria («nephritic flare») (4)
- chronic renal failure (CRF): doubling of serum creatinine lasting for at least 6 months with creatinine clearance <60 ml/min without any improvement over time.
- end stage renal disease (ESRD): the need of dialysis therapy.

The outcome of LN was defined as:

- complete renal remission (normal values of serum creatinine, normal serum albumin and proteinuria <0,25 mg/day)
- partial remission (proteinuria from 0,25 to 2 g/day, together with stabilization or normalization of serum creatinine)
- relapse of disease (an increase in any renal parameter, as serum creatinine by 30%, so called "nephritic flare" or proteinuria by ≥ 30%, as "proteinuric flare").

Treatment failure was defined as a failure to reduce proteinuria by 50% and/or a sustained increase in serum creatinine by >30% (5).

Statistical methods

All data are presented as means ± standard deviation (SD). Statistical differences between arithmetic means of numeric variables of each parameter were assessed using Students' t-test. P value < 0,05 was considered as statistically significant.

Results

Forty one patients with clinical signs of LN were included in the study. Mean patients age was 31,9 ± 12,1 years in the moment of first diagnosis of LN (50% pts under 30 years of age). The female-male ratio was 8:1 in female favor. The mean lupus disease duration before the initiation of therapy was 10,96 ± 6,98 years. Renal disease was pathohistologically verified in 53,7% of patients (4 pts with class III, 17 pts with class IV, one pt with class V of lupus nephritis). The baseline characteristics of lupus nephritis patients are presented in Table 1.

Age (years)	31,9 ± 12,1
Gender (female – male)	36 females and 5 males
Duration of disease (years)	10,96 ± 6,98
Nephrotic syndrome (NS)	22 pts (53,7%)
Acute renal insufficiency + NS	6 pts (14,6%)
Acute renal insufficiency	2 pts (4,9%)
CRF + NS	6 pts (14,6%)
Non-nephrotic proteinuria	5 pts (12,2%)

TABLE 1. The baseline characteristics of lupus nephritis patients

The thirty (30) pts received conventional treatment with cyclophosphamide and corticosteroid. In this group LN was clinically presented as: NS in 19/30 pts, NS associated with ARI in 6/30 pts, only ARI in 2/30 pts and CRF with NS in 3/30 pts. Out of 7 patients, who started treatment with MMF (the first one started three years ago), 3 pts had NS, 3 pts had NS associated with CRF, while 1 pt had non – nephritic proteinuria. Four patients with non – nephritic proteinuria treated only with prednisone.

Average values of proteinuria in the beginning of the treatment were significantly higher in the group of patients treated with pulse doses of CyC (p=0,019), (Table 2). Significant decrease of proteinuria was accomplished in CYC and MMF groups of patients (p<0,001), while the last proteinuric values between these two groups were not significantly different (p=0,80). Average values of serum creatinine between the groups as well as within the groups were not significantly different during the treatment, but the mean serum creatinine was decreased for 30% during the treatment with CyC (p=0,07). Recovery of ARI was achieved in 7/8 pts.

From CyC group, 17 pts achieved complete renal remission (17/30). Nine pts responded to treatment by partial remission, while 3 pts developed end stage renal disease needing dialysis therapy (they started immunosuppressive therapy in CRF). Duration of complete renal remission was 37,3 ± 24,7 months. The mean time until achieving complete remission was 17,2 ± 13,3 months (Table 3).

Five patients from MMF group responded to treatment with complete renal remission, while two developed incomplete remission. Duration of complete remission in this group was 13,0 ± 5,3 months, which was statistically shorter then in CyC group, but the treatment with MMF was started three years ago, and included a small number of patients.

More complication was notified in CyC group of patients, especially infections. During the treatment with CyC one patient died due to cerebrovascular insults (Table 4). During the period of follow up, 29,3% (12) pts developed at least one nephritis flare and were treated again.

Complication	CyC treatment	MMF treatment
infection	27	12
peripheral thrombosis	3	-
CVI	1	-
cataract	1	-
death	1	-

TABLE 4. Complications of therapy

Discussion

Lupus nephritis is one of the most serious manifestations of systemic lupus erythematosus. Treatment of this disease, especially proliferative forms, requires prolonged aggressive therapy, with aim to reduce disease progression and improve long-term outcome of patient with LN. The choice of the therapeutic strategy may have an important role. It is crucial to define regimes that are effective, but with minimum toxicity, both in the short and long term of follow up.

	baseline proteinuria	the last proteinuria	p value	baseline serum creatinine	the last serum creatinine	p value
CyC	5,7 ± 2,41	0,51 ± 0,4	0,0003**	158,0± 129	110,9 ± 45,9	0,07
MMF	2,17 ± 0,98	0,31 ± 0,09	0,004**	105,0 ± 10,5	109,6 ± 6,7	0,10
p value	0,019*	0,80		0,59	0,78	

*p<0,05 **p<0,001

TABLE 2. The baseline and the last average serum creatinine and proteinuria of treated patient

	Cyclophosphamide +Prednisone (30 pts)	Mycophenolate mofetil (7 pts)	Prednisone (4 pts)
Complete remission	17	5	3
Partial remission	9	2	1
Duration of remission (months)	37,3 ± 24,7	13,0 ± 5,3	17,2 ± 4,2
Flare	10	2	-
ESRD	3	-	-
Death	1	-	-

TABLE 3. The response of patient receiving immunosuppressive therapy

Cyclophosphamide in combination with corticosteroid has improved renal survival compared to steroid alone. "NIH protocol" (The National Institutes of Health) of intravenous pulsed cyclophosphamide became the standard for treatment of lupus nephritis (6). Cyclophosphamide is more potent immunosuppressive agent which leads to a good control of the disease. It has improved the prognosis of LN over the years. Cameron found that life expectancy at 5 years increased from 44% in the period 1953-1969 to 82% in the period 1980-1995 (7). In Italian study, which recruited 93 patients who were followed for a median of 15 years, renal survival was 97% at 10 years and 82% at 20 years (8). At the last follow-up visit, 59 patients were in complete renal remission, 18 were in partial renal remission, four patients had chronic renal insufficiency, six had entered end–stage renal disease end six patients had died. In our study mean follow up for all patients was 10,9 ± 4,1 years. The most common clinical manifestation of LN was nephritic syndrome (53,7%). At the last follow-up visit 25/41 pts (60,9%) were in complete renal remission, while 29,2% (12) pts achieved partial renal remission. This happened for period of 17,2 ± 13,3 months from the beginning of the treatment, a time similar to that observed in other studies using different therapeutical schedules (8,9). It was found that many factors influence on renal function of patients with LN. They include the disease-related complications, over or under treatment and toxic effects of immunosuppressive drugs. The prolonged use of these drugs can be loaded with severe and life-threatening complications. The Euro-Lupus Nephritis Trial examined the effects of "low-dose" (3 g) versus "high-dose" (mean of 8,5 g) cyclophosphamide in a randomized study of 90 patients with lupus nephritis (9). Severe infections were more common in the high-dose group, with a trend towards more renal remission in the low-dose group, while the number of renal flare was no different. We treated patients with LN with protocol of "low-dose" pulse of CyC. Despite that, there were more complications as infections in CyC group compared to MMF group.

Risk of chronic renal failure is higher in patients with increased serum creatinine at the time of the first lupus diagnosis. Some of authors found a prognostic role of anemia (10), a high chronicity index at initial renal biopsy (10), role of nephritic flares (11) etc. During our study 29,3% patients developed at least one nephritic flare, which required further vigorous treatment.

Mycophenolate mofetil is a relatively new immunosuppressor with selective inhibitory effects on proliferative T and B lymphocytes. A small number of our patients use this drug because it isn't recovered by financial support from official health policy. Our results confirmed that this drug is also effective in significantly reduce of proteinuria and achievement of renal remission with a smaller prevalence of treatment-related complications. A meta-analysis of randomized controlled trials by Zhu et al. (12) defined that MMF in induction therapy significantly increased the complete remission rate and reduced the risk of infection and leucopenia compared with intravenous CyC. Therefore, the high-dose of corticosteroids remains as the mainstay therapy of LN, with adding a second immunosuppressive agent (such as CyC in induction therapy of life-threatening patients with LN, than MMF in maintenance) to reduce iatrogenic morbidity and keep a wished clinical effects with minimal effective dose of drug.

Conclusion

The most patients with LN achieved partial or complete renal remission using different therapeutical schedules. High percentage of treated patients achieved recovery of acute renal failure. We think that aggressive form of lupus nephritis should be treated by associating cyclophosphamide with corticosteroids therapeutical regiment, but the treatment of this disease must be flexible to the patients and clinical manifestation of disease. MMF is a new promising immunosuppressive drug for a treatment of this serious disease.

List of Abbreviations

ESRD	-	end stage renal disease
CRF	-	chronic renal failure
LN	-	lupus nephritis
NS	-	nephrotic syndrome
GFR	-	glomerular filtration rate
MMF	-	mycophenolate mofetil
CyC	-	cyclophosphamide

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