NEFROLOGÍA. Volumen 27. Número 1. 2007

ORIGINALS

Intravenous Cyclophosphamide for lupus nephritis: twenty years reducing the dose

M. A. Frutos[1], A. Martín Gómez[1], E. de Ramón[2], M. T. Camps[2], A. Valera[5], I. García[3] and A. Fernández Nebro[4]

[1]Nephrology. [2]Internal Medicine. [3]Phatology. [4]Rheumatology. Carlos Haya University Hospital. [5]Nephrology. Virgen de la Victoria University Hospital.

SUMMARY

The prognosis for patients with proliferative glomerulonephritis associated with systemic lupus erythematosus has dramatically improved over recent decades. We review our experience with intermittent pulse therapy with intravenous cyclophosphamide (IC) in 97 patients (75 female) aged over 20 years. The series was divided into three groups. Group A (n = 39) received monthly IC pulses (begin 1 g) for up to 24 months between 1985-1991. Group B (n = 47) received monthly IC pulses (1 g) for six months with additional quarterly doses for a maximum of 18 months, depending on the therapeutic response (from 1991). From 1999, Group C (n = 11) patients were treated with low-dose IC (3 g in three months) followed by azathioprine (2 mg/kg) or mycophenolate mofetil (1.5-2.0 g/day) for 12-18 months. The total IC doses (g) administered were: Group A, 15.1 ± 9.0; Group B, 8.5 ± 3.5; and Group C, 3.0 ± 0.0. These figures show the trend towards progressive reduction in exposure to IC. Overall, treatment with the different IC regimens achieved satisfactory control of lupus nephritis in 76% of the patients. Comparison of the values at baseline and after 24 months showed that the serum creatinine (mg/dl) fell in Group A from 1.77 ± 1.06 to 1.09 ± 0.63, in Group B from 1.22 ± 0.85 to 0.95 ± 0.45, and in Group C from 0.90 ± 0.23 to 1.17 ± 0.54 ($p < 0.05$). In the same period, proteinuria (g/day) fell in Group A from 6.19 ± 4.31 to 0.79 ± 1.76, in Group B from 4.43 ± 3.17 to 2.08 ± 3.65, and in Group C from 5.43 ± 3.37 to 3.22 ± 4.00 ($p < 0.05$). There was not differences between the three groups in both variables. The adverse effects were mainly viral and bacterial infections, with no intergroup differences. Avascular osteonecrosis requiring hip replacement and early menopause were more frequent in Group A. Nine patients died, seven due to cardiovascular causes and two with infection. No differences were detected between the three groups when analyzing the overall patient survival at 5, 10 and 15 years (95%, 92%, and 84%, respectively). The likelihood of maintaining serum creatinine within normal ranges or less than twice the baseline range was similar in the three groups at 5, 10 and 15 years (92%, 72% and 66%, respectively). There were 47 episodes of relapse, with no differences between the three groups. In summary, treatment with different regimens of intermittent IC is relatively safe and efficient to control the disease and lupus nephritis in SLE patients even with progressively smaller doses. The price paid concerned infectious complications, and bone and ovarian toxicity. New alternatives

Correspondence: Miguel Frutos
E-mail: mfrutoss@senefro.org

should at least maintain the same efficacy, but with fewer adverse effects and relapses.

Key words: ***Systemic Lupus Erythematosus. Cyclophosphamide. Lupus Nephritis.***

CICLOFOSFAMIDA INTRAVENOSA EN NEFRITIS LÚPICA: VEINTE AÑOS REDUCIENDO DOSIS

RESUMEN

El pronóstico de la afectación renal en pacientes con lupus eritematoso sistémico (LES) ha mejorado notablemente en las últimas décadas. Se revisa la experiencia de tratamiento con pulsos de ciclofosfamida intravenosa (CFiv) en el tratamiento del primer brote de nefritis lúpica en 97 pacientes (75 mujeres) seguidas durante un periodo de hasta 20 años. La serie se ha dividido en tres grupos. El Grupo A (n = 39) recibió pulsos mensuales de CFiv (inicio de 1 g) durante un periodo de hasta 24 meses (años 1985-1991). El Grupo B (n = 47) recibió pulsos de CFiv (1 g) mensuales durante 6 meses con pulsos adicionales trimestrales hasta un máximo de 18 meses, dependiendo de la respuesta terapéutica (desde 1991). A partir de 1999 un grupo de 11 pacientes se trataron con pulsos de CFiv a dosis bajas (pauta Eurolupus Nephritis Trial), 500 mg cada 15 días durante tres meses, seguidos de azatioprina (2 mg/kg) o micofenolato mofetil (1,5-2,0 g/dia) hasta completar 36 meses de tratamiento (Grupo C). La cantidad total de CFiv (g) administrada: Grupo A: 15,1 ± 9,0; Grupo B: 8,5 ± 3,5 y Grupo C: 3,0 ± 0, muestra la tendencia hacia una progresiva disminución en la exposición a la ciclofosfamida. Globalmente, los tratamientos con las diferentes pautas de CFiv consiguieron en primera intención, controlar la nefritis lúpica de forma satisfactoria en el 76,3% de los casos. Al comparar los valores basales y los alcanzados a los 24 meses, la creatinina sérica (mg/dl) pasó en el grupo A desde 1,77 ± 1,06 a 1,09 ± 0,63; Grupo B: 1,22 ± 0,85 a 0,95 ± 0,45 y Grupo C: 0,90 ± 0,23 a 1,17 ± 0,54 (p < 0,05). No se detectaron diferencias entre los tres grupos. Para los mismos periodos la proteinuria (g/día) descendió en el grupo A desde 6,19 ± 4,31 a 0,79 ± 1,76; Grupo B: 4,43 ± 3,17 a 2,08 ± 3,65 y Grupo C: 5,43 ± 3,37 a 3,22 ± 4,00 (p < 0,05). Los efectos adversos fueron principalmente infecciones víricas y bacterianas, sin diferencias intergrupos. La necrosis ósea avascular con necesidad de prótesis y menopausia precoz fueron más frecuentes en el Grupo A. Nueve pacientes fallecieron, siete por enfermedad cardiovascular y dos por infección. La supervivencia global de los pacientes en los tres grupos de tratamiento no mostró diferencias significativas siendo del 95% (IC 95%: 99%-90%) a los 5 años; del 92% (IC 95%: 98%-85%) a los 10 años y del 84% (IC 95%: 94%-74%) a los 15 años. La probabilidad de mantener concentraciones de creatinina sérica en rango normal o inferior al doble de la basal fue del 92% (IC 95%: 98%-86%) a los 5 años; del 72% (IC 95%: 84%-60%) a los 10 años y del 66% (IC 95%: 78%-54%) a los 15 años, sin detectarse diferencias significativas entre los tres grupos de tratamiento. Se contabilizaron 47 episodios de recidivas sin diferencias entre los tres grupos. A modo de conclusión, esta experiencia con diferentes estrategias de CFiv muestra que es una terapia eficaz en controlar la nefritis lúpica y mantener la vida en pacientes con nefritis lúpica, incluso con dosis progresivamente menores. El precio a pagar está relacionado con complicaciones infecciosas y de toxicidad en huesos y gónadas. Nuevas alternativas terapéuticas deberán mantener al menos la misma eficacia con menor tasa de efectos adversos y recidivas.

Palabras clave: ***Lupus eritematoso sistémico. Ciclofosfamida. Nefritis lúpica.***

INTRODUCTIÓN

Lupus nephritis is the most frequent severe visceral condition affecting patients diagnosed with systemic lupus erythematous (SLE). In prospective studies it is present in up to 39% of all patients and almost half of young patients.[1] In some cases, the presence of acute renal failure (ARF) is a feature present at the disease diagnosis.[2] Considered separately, lupus nephritis represents the indicator of visceral involvement best correlating with global survival from the disease.[3] Until de 1970s, half of the patients with sever lupus nephritis died or underwent dialysis within few years from diagnosis. The prognosis has notably improved nowadays due to advances in early SLE diagnosis, and global therapy and management of its complications.[4,5] The varied presentations and the multiplicity of pathologies accounting for renal failure[6] require urgent diagnostic actions in order to assess the degree of renal involvement and readily implement the most convenient therapy.[7] In the cases of severe lupus nephritis being categorized as proliferative glomerulonephritis and in some membranous types, the first therapeutic goal should be preserving life and slow renal and systemic disease. Then, it is necessary to plan renal function protection in the long run and detecting and early treating the recurrences.[8] Remission induction therapy with cytotoxic immunosuppressants has been considered as the first line therapy by several groups[9-11], including ours,[12] by applying several therapeutic strategies that have been modified with time.[13] The present study assesses the experience of a multidisciplinary group with a large series of patients diagnosed with severe lupus nephritis treated at the time of diagnosis with intravenous cyclophosphamide (ivCP) pulses as the first option. By including also a prolonged follow-up, this experience is rendered interesting by showing that CP efficacy is maintained in spite of progressively reducing the dose of this immunosuppressive agent and at a time when the risk-benefit ratio of ivCP therapy is being questioned due to the emergence of novel effective therapeutic alternatives, during both the induction and maintenance phases, and apparently better tolerated.[14-16]

PATIENTS AND METHODS

Ninety-seven patients (75 women) diagnosed with SLE according to the American College of Rheumatology criteria[17] were studied between 1985 and 2004. All were studied and treated by nephrologists, rheumatologists, and internists at two reference hospitals in Malaga. The action plan regarding diagnostic and therapeutic criteria was set following the National Institutes of Health (NIH) therapeutic action plan.[10] The decision of performing renal biopsy at the time of diagnosis was considered in 90 patients (92.7%) for having analytical changes suggesting renal involvement (proteinuria, hematuria or glomerular filtration deterioration). In seven patients, renal biopsy was not available because of: lack of adequate equipment, lack of consent, or medical contraindication. Renal biopsies were performed locating the lower pole by real time ultrasounds and with a gun-type automated device. Generally three cylinders were obtained that were processed for light microscopy (hematoxylin-eosin, PAS, and Masson's trichromic), immunofluorescence and electronic microscopy, all biopsies being evaluated by the same pathologist. All patients with type IV (WHO classification[18]) renal involvement and type III with nephrotic proteinuria or acute nephritic syndrome and type V with proteinuria > 3.5 g/day were included into treatment protocols with ivCP pulses. Patients treated between 1985 and 1991 (n = 39) received monthly ivCP pulses on an intention-to-treat schedule continuously for 24 months (Group A). By the end of 1991, the trend was to decrease the exposure time to CP in a way that patients received 6 ivCP pulses within the following months and then quarterly intention-to-treat pulses for 18 additional months according to response to treatment (n = 47) (Group B). Finally, since 1999, progressively although not exclusively treatment schedules were started with 500 mg ivCP pulses administered fortnightly for three months and followed by azathioprine (2 mg/Kg) or mycophenolate mofetil (1.5-2.0 g/day) until completing 36 months of treatment (n = 11) (Group C).

Objectives

To achieve control of baseline disease (clinical symptoms and activity laboratory data) as the starting point to normalize renal function impairments such as proteinuria or elevated serum creatinine.

IvCP pulses

ivCP pulses were given at the hospital in the morning at an initial dose of 1 g diluted into 250 mL of 0.9% saline and infused during 60 min (Groups A and B). In order to reduce the risk for hemorrhagic cystitis 1000 cc of normal saline were previously administered for 90 min (except for arterial hyper-

tension cases or very edematous patients in whom the same volume of 5% dextrose was administered).As 24-h premedication before ivCP pulses, we recommended the intake of 2 liters of water for forcing diuresis and anti-emetics such as metoclopramide 10 mg t.i.d. and sedatives such as lorazepam 2 mg t.i.d. For 24 hours patients were encouraged to increase oral fluids to a volume greater than 2 liters and using the same anti-emetics. In recent years, ondansetron has been occasionally used as anti-emetic. No patient received Mesna. All patients received prophylaxis with trimethoprim- sulfamethoxazole 80/400 mg/day during prescription of ivCP.Successive doses of ivCP depended on the leukocytes nadir 7-10 after CP administration and were generally increased by 10% (up to a maximal dose of 1600 mg/pulse) provided that total leukocyte count was within the normal range and were reduced by 10% when the leukocyte nadir did not reach 3000/mm^3. In renal failure patients, the initial ivCP dose was reduced to one half. All patients were instructed on early detection if infections and urgent consultation if symptoms of fever, infection or bleeding were present.

Corticosteroids

Initially 3 pulses of 500 mg of 6-methyl-prednisolone for three consecutive days were administered only in those cases having one of the following circumstances: a) acute renal failure, b) sings of severe systemic SLE involvement, and c) nephrotic syndrome. Then, all patients received prednisone 1 mg/Kg/day for the first month; 0.6 mg/Kg/day the second month; 0.4 mg/Kg/day the third month; 0.3 mg/Kg/day the fourth month; 0.25 mg/Kg/day the fifth month; and 0.2 mg/Kg/day as the maintenance dose (approximately 15 mg/day).

Childbearing age women

They were informed about the impossibility of pregnancy during the time of administration of cyclophosphamide and about the use of some sort of efficacy proven contraceptive method.

Remission

Complete remission of lupus nephritis was considered when proteinuria decreased to less than 500 mg/day, the presence of non-active sediment, and normalization or stabilization of GFR.

Recurrence

Recurrence diagnosis was based on the presence of at least two laboratory changes: a) Increase of anti-DNA antibody titers; b) increase of proteinuria (by more than 50%) and active sediment (more than 8 red blood cells and/or 6 leukocytes per filed); c) hematological impairments (leukopenia, lymphopenia, anemia); d) C3 and C4 decreases.

Renal function survival

Time elapsed between ivCP treatment onset and doubling serum creatinine baseline level or entry into dialysis.

Statistical analysis

statistical data are shown as mean ± standard deviation (SD) and as absolute and relative frequencies. For comparison of baseline features between the three treatment groups one-factor ANOVA test for quantitative variables and the chi-squared test for qualitative variables were used. For comparison of results obtained in the three treatment groups with time, ANOVA test for repeated measurements was used with the different determinations taken during the follow-up (baseline, 6, 18, and 24 months) being the intra-group factor and the type of treatment (groups A, B, and C) the inter-group factor. The analysis included polynomial a priori contrast in order to assess the trend of laboratory changes with time. In order to assess the importance of differences existing between groups at the beginning of the study, the interaction between the variables time and treatment group was introduced into the model. To assess the changes occurred in the sediment (from active to non-active) with time, the Cochran Q test was used. Survival functions were calculated by the Kaplan-Meier analysis by using the Log-rank test to assess statistical significance. A probability with an alpha error lower than 5% at two-tailed tests was considered to be significant.

RESULTS

A first evaluation of the study groups into which patients have been categorized shows similar age and gender values (Table I). In group A, treated with the long ivCP schedule, the renal involvement profile predominantly included patients with type IV lupus nephritis; by contrast, patients treated in later years

showed a greater percentage of focal proliferative and membranous types. As for activity indexes, group B showed values significantly lower than those in groups A and C. There were no significant inter-group differences by chronicity indexes, in all groups being closed to 1. The presence of arterial hypertension (AHT) was more frequent in groups B and C (49.5% and 54.5%, respectively). The percentage of patients treated with ACEIs or ARA-II has been progressively increasing as the treatment period advances. The differences in the total amount of ivCP administered has been important, in such a way that group B received approximately a little bit more than half the dose and group C a fifth of the dose than group A did. Table II shows the evolution of some the parameters of renal function and general activity of the disease for the first two years of treatment and patients' follow-up. In broad terms, ivCP therapy achieved normalization of SLE immunological activity parameters (C3 and anti-DNA) and could be classified as effective for lupus nephritis management in 76.3% of the patients. The decrease of blood creatinine levels and proteinuria occurred within the first 6 months of treatment, especially in group A, stabilizing later on. Group A had greater creatinine levels at the beginning of the study, reaching similar levels to groups B and C at the end (significant interaction between time and treatment groups; $p < 0.005$). By contrast, all three groups had similar proteinuria levels at the beginning of the study, but there was higher normalization of them at the end of the study in group A (significant interaction between time and treatment groups; $p < 0.05$). The sediment changed from active to non-active with time in all treated patients. In the analysis by groups, a progression to inactive sediment was also observed in groups A and B ($p < 0.05$) and a trend, although not significant, in group C ($p = 0.14$). C3 blood levels also changed towards normality within the first 6 months, stabilizing later on. C4 blood levels also increased with time, following a similar profile than the above variables, although not reaching statistical significance. Anti-DNAn antibody levels also decreased within the first 6 months with a mild increase after stabilization (statistical significance for cubic polynomial contrasts; $p < 0.05$).Among the main side-effects occurred during this treatment period, from minor to major importance, we should highlight gastrointestinal side-effects suffered in varying degrees of severity by half of the patients, although they did not account for a significant number of CF therapy withdrawals. When vomiting was severe or prolonged, anti-emetic premedication included ondansetron with no objective data supporting this action. Other adverse effects such as alopecia were always transient and without consequences. Table III shows other notable complications suffered by the patients in this series. Most of infections were bacterial in nature. There were 3 diagnosed neoplasms: breast, myometrium, and non-Hodgkin lymphoma. Fifteen patients had avascular necrosis of the femur head (two also at the humerus head) all of them requiring prosthetic replacement. The number of female patients with persistent post-treatment menstrual impairments and classified as early menopause was 9 (31.0 %) in Group A; 4 (10.2%) in Group B and none in Group C ($p = 0.02$).Table IV summarizes the clinical situation of all treated patients at closure of the study or exitus. As for evidenced recurrences, 47 recurrence events were documented with no percentage differences between groups. 54.5% of all recurrence episodes occurred within the following two years of ending ivCP administration. Patients' survival in the three treatment groups did not show significant differences (Figure 1) (Log-rank: 1.15; $p = 0.56$), being 95% (95% CI: 99%-90%) at 5 years; 92% (95% CI: 98%-85%) at 10 years, and 84% (95% CI: 94%-74%) at 15 years, res-

Table I. Baseline characteristics of treated patients

	Group A (n = 39)	Group B (n = 47)	Group C (n = 11)	p
Age (years)	29.7 ± 10.3	27.9 ± 10.0	32.1 ± 12.9	NS
Gender (M/F)	10/29	8/39	4/7	NS
AHT, N (%)	29 (74.2)	23 (49.5)	6 (54.5)	NS
ACEIs/ARA-II, N (%)	8 (20.5)	15 (31.9)	6 (54.5)	0.05
Biopy Types III/IV/V (WHO)	5/32/1	11/23/7	4/2/5	0.05
Activity index (Austin[30])	10.5 ± 3.3	8.2 ± 3.2	11.7 ± 0.6	0.01
Chronicity index (Austin[30])	1.1 ± 1.3	0.9 ± 0.9	0.0 ± 0.0	NS
Administered ivCP (g)	15.1 ± 9.0	8.5 ± 3.5	3.0 ± 0.0	0.00

* Statistical inter-group significance after applying ANOVA, Kruskal Wallis or χ^2 tests ($p < 0.05$).
M: Male; F: Female; AHT: Arterial hypertension.
ACEI: Angiotensin converting enzyme inhibitors.
ARA-II: Angiotensin II receptor antagonists.
ivCP: intravenous cyclophosphamide.

pectively. Nine patients died, seven from cardiovascular causes (ischemic heart disease in six and dilated cardiomyopathy and pericarditis in one) and two from infection (CMV sepsis and polymicrobial pancreatitis-peritonitis).The likelihood of maintaining serum creatinine levels within the normal range or lower than twice the baseline ones was 92% (95% CI: 98%-86%) at 5 years; 72 % (95% CI: 84%-60%) at 10 years, and 66% (95% CI: 78%-54%) at 15 years, respectively (Figure 2), with no significant differences

Table II. Analytical changes observed after administration of ivCP pulses including baseline (b), and at 6, 18 and 24 months of follow-up determinations

	SCr (mg/dl) ✣❁✷#	Proteinuria g/day ✣✷#Δ♠	C3 (mg/dl) ✣#	C4 (mg/dl) ✷	1/anti-DNA ✣ϕ
Group A_b	1.77 ± 1.06	6.19 ± 4.31	52 ± 22	13 ± 10	174 ± 166
Group B_b	1.22 ± 0.85	4.43 ± 3.17	50 ± 22	9 ± 4	171 ± 165
Group C_b	0.91 ± 0.23	5.43 ± 3.37	70 ± 23	10 ± 2	113 ± 125
$Total_b$	1.43 ± 0.96	5.23 ±3.74	52 ± 23	10 ± 7	166 ± 160
Group A_6	1.15 ± 0.60	1.86 ± 1.99	80 ± 20	16 ± 7	41 ± 74
Group B_6	0.92 ± 0.36	1.61 ± 1.73	85 ± 30	16 ± 9	58 ± 84
Group C_6	0.86 ± 0.21	2.87 ± 2.55	82 ± 25	15 ± 4	23 ± 32
$Total_6$	1.01 ± 0.48	1.82 ± 1.93	83 ± 25	16 ± 8	49 ± 77
Group A_{18}	1.15 ± 0.73	0.92 ± 1.68	85 ± 18	16 ± 6	49 ± 102
Group B_{18}	0.85 ± 0.37	1.28 ± 1.46	85 ± 29	15 ± 14	72 ± 97
Group C_{18}	1.10 ± 0.61	1.77 ± 1.80	97 ± 60	27 ± 31	28 ± 65
$Total_{18}$	1.00 ± 0.50	1.18 ± 1.58	86 ± 30	17 ± 15	60 ± 96
Group A_{24}	1.09 ± 0.63	0.79 ± 1.76	91 ± 26	19 ± 11	38 ± 84
Group B_{24}	0.95 ± 0.45	2.08 ± 3.65	81 ± 27	14 ± 9	79 ± 116
Group C_{24}	1.17 ± 0.54	3.22 ± 4.00	88 ± 38	19 ± 10	58 ± 128
$Total_{24}$	1.00 ± 0.54	1.66 ± 3.13	85 ± 28	16 ± 10	64 ±108

Statistical analysis by repeated measurements ANOVA at the beginning and at 6, 18 and 24 follow-up months. The variable treatment group was included as the inter-subject factor.
✣ Significación in intra-groups contrasts ($p < 0.05$).
❁ Significance in inter-group contrasts ($p < 0.05$).
✷ Interaction between the variable time and group ($p < 0.05$).
Significance in a priori squared polynomial intra-group contrast ($p < 0.05$).
Δ Patients treated with ACEIs/ARA II had greater proteinuria decrease during the follow-up ($p < 0.05$).
♠ The sediment changed from active to non-active in the whole treated patients ($p < 0,05$). In the group analysis, a progression towards sediment inactivity was observed in groups A and B ($p < 0.05$) and a similar trend in group C ($p = 0.14$).
ϕ Significance in a priori cubic polynomial intra-group contrast ($p < 0.05$).

Table III. Main adverse effects presented by patients in each one of the ivCP-treated groups

	Group A	Group B	Group C	p
Herpes zoster, N (%)	5 (12.8)	5 (10.6)	1 (9.0)	
Bacterial pneumonia, N (%)	1 (2.5)	2 (4.2)*	1 (9.0)	NS
Urinary tract infection, N (%)	8 (20.5)	7 (14.8)	3 (27.0)	
Sepsis, N (%)	0	1 (2.1)	0	
Avascular bone necrosis, N (%)	8 (20.5)	6 (12.7)	1 (9.0)	0.05
Premature menopause, N (%)	9 (31.0)	4 (10.2)	0	0.02
Hemorrhagic cystitis, N (%)	0	0	0	–
Neoplasia, N (%)	1 (2.5)	2 (4.2)	0	NS

* One TB pneumonia.

being observed between the treatment groups (Log-rank test: 1.56; (p = 0.46)). In the Cox proportional hazards multivariate regression analysis, which included the treatment group as the main predictive variable, those variables not homogenously distributed among the groups (baseline serum creatinine, nephritis histological type, Austin histological activity index, and treatment with ACEIs/ARA-II, or proteinuria, that did not show baseline differences) did not have an influence on patients' survival or renal function survival (data not shown). Finally, the histological chronicity index (RR: 2.5; 95% CI: 1.4-4.3), and to a lesser extent the histological activity index (RR: 1.4; 95% CI: 0.95-1.9) determined the progression towards renal failure although none of them had an influence on patients' overall survival.

DISCUSSION

Cyclophosphamide therapy in patients with lupus nephritis started to be relevant in the 1970s from the studies performed at the Mayo Clinic,[19] initially administered p.o. and always associated to steroids. The regimens and drug combinations were at the beginning very diverse,[20] occasionally combined to or followed by azathioprine aiming at reducing toxicity. Further, oral CP was substituted by intermittent pulses of ivCP, the experience from the NIH studies being the most conclusive on the long-term advantages about the lower progression to renal failure and lower recurrence rates.[10] From these experiences, the administration of monthly ivCP pulses together with oral steroids has been proposed as the most effective com-

Table IV. Clinical condition of all treated patients at the end of the study

	Group A	Group B	Group C	p
Renal function	Normal serum Cr or lower than twice the baseline one	24	39	10
	CRF with serum Cr more than twice the baseline one	3	4	1
	Hemodialysis	8	2	0
Evolution	Transplanted	2	1	0
	Lost to follow-up	2	1	0
	Exitus			
	– Cardiovascular	3	4	–
	– Infection	1	1	–
	Recurrences, N (%)	19 (49)	23 (49)	5 (45)

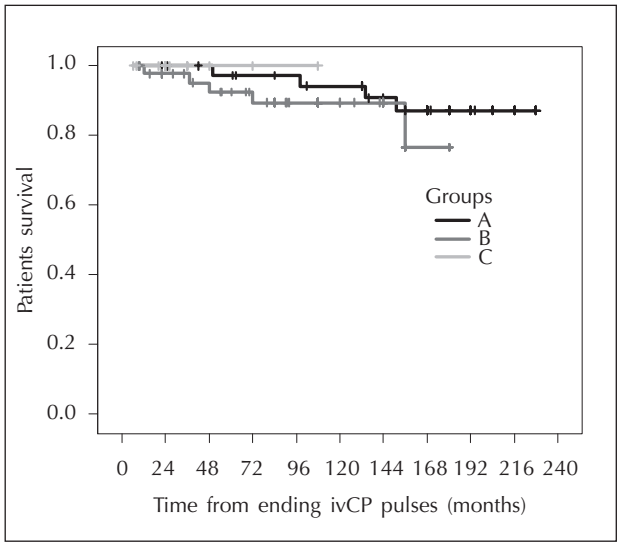

Fig. 1.—Patient survival by ivCP administration regimen (Log rank = 1.15, p = NS).

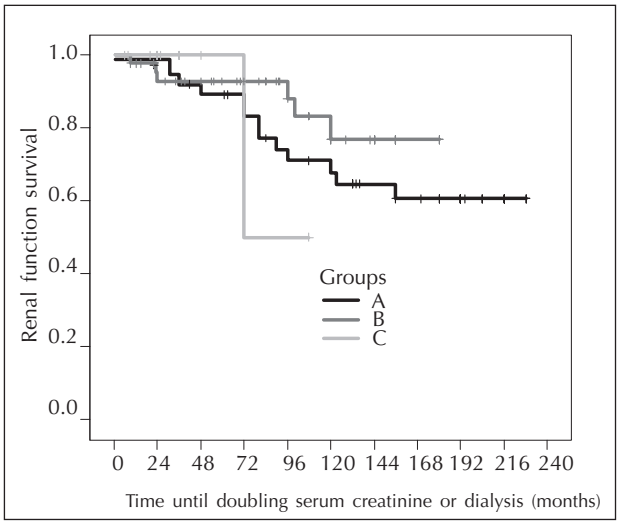

Fig. 2.—Renal function survival. patients within each one of the three groups that maintain normal sCr or lower than twice the baseline one and have not reached dialysis therapy. Log rank = 1.56, p = NS).

bination to control lupus nephritis progression.[21] The use of ivCP pulses has been the first choice therapy for severe lupus nephritis cases.[22] This 20-year experience with the use of ivCP in patients with lupus nephritis has run parallel to the global tendency to use lower and lower CP doses[23] looking for the greatest benefit with the lowest risk. This review aims at transmitting globally satisfactory outcomes before closing what seems to have been the best immunosuppressive therapy period for patients with severe lupus nephritis.

Performance of renal biopsy in almost every case in this series is in agreement with the usual practice of Spanish nephrologists since lupus nephritis is the most frequent biopsied secondary nephropathies.[24] In such an objective way, we may document the severity of the renal damage and rigorously ask for informed consent for ivCP therapy. The new classification of renal involvement in lupus, which broadens subtypes III and IV by better classifying predominant segmentary or global changes,[25,26] may facilitate future interpretations of therapeutic responses or prognosis of renal function. Besides helping with the initial diagnosis, renal biopsy is of great interest also in situations with acute renal failure[27] and whenever there is doubt on the therapeutic approach. In this way, whether immunosuppressive therapy has to be maintained, increased or withdrawn is better solved.[28,29]

The difference between the two types of lupus nephritis included in this work during the 1990s or 2000s reflects the better knowledge and greater confidence acquired with the use of ivCP, an instance that conditioned the inclusion of patients with focal proliferative or membranous lupus nephritis types that would have not been considered previously.

The low chronicity indexes of this series are explained by the fact that all patients are diagnosed and treated at their first episode. It is likely that this circumstance may have had a positive influence on the good response to ivCP pulses. Its prognostic value seems to be higher than that reported for activity indexes since for values higher than 3 the likelihood of regression of the lesions is considerably lower,[30,31] our series confirming that the RR for progression to chronic renal failure was correlated with the histological chronicity index.

Throughout the years, total ivCP doses have been progressively lower and, in any case, adjusted to the experience and caution although considering that relatively short ivCP treatments may be associated to a greater number of recurrences and prolonged ones could be responsible of greater side effects. The main change took place when the duration of the so-called induction period was reduced from 24 to 6 months, this modification facilitating the segregation of the whole sample into groups A and B.

By the end of 1991, patients received quarterly additional doses for 12-18 months, in a phase that we call today maintenance phase seeking the consolidation of the effects achieved with higher ivCP doses administered during the induction phase and preventing recurrences. Within the last five years, it has been proposed to further reduce the time of administration of ivCP or even replacing it during the maintenance phase by other drugs such as azathioprine or mycophenolate mofetil, these latter having similar efficacy and higher safety. Adhering to a non renounceable principle of decreasing complications, this philosophy was applied to patients included in our Group C. In any case, optimal duration of ivCP therapy for lupus nephritis as well as the doses still is currently a matter of debate.

The benefits achieved in this series with regards to renal function have been notable for proteinuria reduction and normalization of serum creatinine. The different ivCP regimens have achieved important and significant decreases in 24-h proteinuria. Most of the patients have reached complete remission with proteinuria lower than 500 mg/day and non-active sediment. However, certain degree of proteinuria of around 1 g/day has been a constant in many patients, particularly those with type V (WHO) disease. When that proteinuria was not associated to microhematuria and serological controls for SLE showed no activity, this was interpreted as being secondary to the glomerular scarring process after acute inflammatory damage. It seems evident that, regarding proteinuria, the less the better and, in this sense, continuous administration of ACEI or ARA-II, alone or in combination, should be contemplated according to tolerance in most of the patients with lupus nephritis showing renal function impairments.[32,33] The decrease in proteinuria achieved was significantly higher in patients treated with ACEIs or ARA-II independently of the treatment group, although we should point out that patients receiving these drugs had higher levels of proteinuria.

Among the main goals when planning a therapy with immunosuppressants in SLE patients, the essential one is to achieve patient's survival. Evidently ivCP is an aggressive therapy, as lupus disease and secondary lesions in important organs such as the kidney are. This 20-year experience with ivCP pulses shows it is an effective therapy, it preserves life, maintains stable creatinine serum levels or within the normal range, decreases proteinuria, and stops active sediment, the price having to paid to achieve these goals is assumable taking into account the risk-benefit ratio.

However, so evident outcomes have not been found in all the series. These differences are due to

other factors including socioeconomic and ethnic.[34,35] Thus, disagreements on side effects of ivCP pulses between north American and European or Asian series have been shown in some studies. Even within the same country, such as the USA, identical regimens with ivCP pulses have produced very different side effects according to the socio-demographic profile of included patients. This one of the controversial aspects that have lead to debate with regards to ivCP therapy.[36] The follow-up to which these patients must be submitted in order to prevent infectious complications or early detecting tumoral ones as well as minimizing toxicity risks on other organ systems is paramount and may, in the absence of other variables, explain the differences.

From a general point of view, this experience confirms that patients treated during this broad period with one of the three protocols reach an excellent global survival and most of them (83%) preserve their own renal function without dialysis or transplantation. With regards to gonadal toxicity, side effects of ivCP pulse therapy were significant, the total dose of CP being the factor determining ovarian toxicity independently of oral or intravenous administration.[37] Transient menstrual changes or premature menopause are important complications deteriorating quality of life and preventing gestations once disease remission has been achieved, and conditioning a greater level of osteopenia and cardiovascular risk.[38,39] In this sense, concomitant treatments with statins, oral calcium supplements, and angiotensin II inhibitors / ARA II blockers should be recommended to lupus patients. The use of biphosphonates might bring additional and interesting advantages.

The concern for infections has been a constant. The most severe viral ones have been from the Herpes group, some of them very virulent with painful sequelae. Infections such as pneumonia have been relatively less frequent and with good therapeutic response. As a whole, it may be stated the incidence of infectious complications has been low, with is in disagreement with other studies.[4,40] It is in these situations where alternative therapies with mycophenolate mofetil that seem to be effective for both the induction and the maintenance phases and with less side effects[14,15,16,41] will be more and more relevant. Therefore, in the future there will be a trend to include or consolidate therapies with different mechanisms of action so that using lower doses of each agent the maximal benefit may be attained with the lowest side effects, both in the short and in the long terms.

A usual concern when treating patients with SLE and severe LN is the possibility of disease recurrence, how to early detecting and treating it. Usually it occurs during the months of lower immunosuppression, however, late recurrences are not exceptional.[42,43]

Their incidence ranges 27-66% according to several studies.[44] Our rate has been within this range. When recurrences are mild, sometimes doubtful, just increasing the steroid dose may be sufficient. Other times, the administration of other immunosuppressants is the rule.[45] In the past, our group predominantly made use of additional ivCP pulses. In the present time, the use of azathioprine or mycophenolate mofetil to control recurrences in cases previously treated with ivCP seems to be appropriate according to the tolerability profile shown in several studies.[46] For membranous forms that usually don't go into remission so well with ivCP, the experience reported in some series with cyclosporin has achieved remissions in patients refractory to ivCP pulses.[47]

In conclusion, this experience with ivCP pulses has been an effective therapy in patients with SLE and severe LN. Progression to more individualized administration regimens with lower cumulative doses of CP has achieved high rates of remission, patients' survival, and renal function preservation. The adverse effects occurred due to immunosuppression may be considered as tolerable within the risk-benefit scenario. It is time for reflection on the present and future of ivCP.[48] In any case, ivCP pulses are kept as the first therapeutic option for new patients with severe lupus nephritis. However, and while other alternatives consolidate, patients with moderate nephritis and good renal function[49] may benefit from immunosuppressive regimens yielding the same efficacy than ivCP pulses with better safety profile.

REFERENCES

1. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, Aydintug AO, Chwalinska-Sadowska H, De Ramón E, Fernández-Nebro A, Galeazzi M, Valen M, Mathieu A, Houssiau F, Caro N, Alba P, Ramos-Casals M, Ingelmo M; Hughes GR: European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine* (Baltimore) 82: 299308, 2003.
2. Frutos MA, Calvar C, Valera A, Cabello M y López de Novales E. Insuficiencia renal aguda en la nefritis lúpica. *Nefrología* 12: 140-146, 1992.
3. Arce-Salinas CA, Villa AR, Martínez-Rueda JO, Muñoz L, Cardiel MH, Alcover-Valera J, Alarcón-Segovia D. Factors associated with chronic renal failure in 121 patients with diffuse proliferative lupus nephritis: a case-control study. *Lupus* 4: 197-203, 1995.
4. Fiehn C, Hajjar Y, Mueller K, Waldherr R, Ho AD, Andrassy K. Improved clinical outcome of lupus nephritis during the past decade: importance of early diagnosis and treatment. *Ann Rheum Dis* 62: 435-439, 2003.
5. Cameron JS. Lupus nephritis. *J Am Soc Nephrol* 10: 413-424, 1999.

6. Lewis EJ, Schwartz MM. Pathology of lupus nephritis. *Lupus* 14: 31-38, 2005.
7. Ginzler EM, Moldovan I. Systemic lupus erythematosus trials: successes and issues. *Curr Opin Rheumatol* 16: 499-504, 2004.
8. Balow JE. Clinical presentation and monitoring of lupus nephritis. *Lupus* 14: 25-30, 2005.
9. Gil CM, Rivera F, Crespo A, Egea JJ, Gil MT, Olivares J. Evolución de la nefritis lúpica grave tratada con ciclofosfamida parenteral y esteroides orales. *Nefrología* 19: 514-521, 1999.
10. Austin HA 3rd, Klippel JH, Balow JE, le Riche G, Steimber AD, Plotz PH, Decker JL. Therapy of lupus nephritis. Controlled trial of prednisone and citotoxic drugs. *N Engl J Med* 314: 614-619, 1986.
11. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastián GD, De Ramón E, Danielli MG, Abramovicz D, Blockmans D, Mathieu A, Direskenelli H, Galleazi M, Gul A, Levy Y, Petera P, Popovic R, Petrovic R, Sinico RA, Cattaneo R, Font'-Depresseux G, Cosyns JP, Cervera R. Immunosuppresive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial. A randomized trial of low-dose *versus* high dose intravenous cyclophosphamide. *Artritis Rheum* 46: 2121-2131, 2002.
12. Frutos MA, Rivilla A, García I, Burgos D, Valera A, Martín-Reyes G, Cabello M, López de Novales E. Tratamiento con ciclofosfamida intravenosa del lupus eritematoso sistémico severo. *Nefrología* 10: 88-93, 1990.
13. Mok CC, Ho CT, Siu YP, Chan KW, Kwan TH, Lau CS, Wong RW, Au TC. Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens. *Am J Kidney Dis* 38: 256-264, 2001.
14. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, Lau CS, Wong AK, Tong MK, Chan KW, Lai KN. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 343: 1156-1162, 2000.
15. Contreras G, Pardo V, Leclercq B, Lenz O, Tozman E, O'Nan P, Roth D. Sequential therapies for proliferative lupus nephritis. *N Engl J Med* 350: 971-980, 2004.
16. Ginzler E, Dooley MA, Aranow C, Kim MY, Buyon J, Merill JT, Petri M, Gilkeson GS, Wallace DJ, Weisman MH, Appel GB. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 353: 2219-2228, 2005.
17. Hochberg MC. Updataing the American College of Rheumatollogy revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 40: 1725, 1997.
18. Churg J, Sobin LH. Lupus nephritis. En: Churg J, Sobin LH eds.: Renal disease, classification and atlas of glomerular diseases. New York, NY, Igaku-Shoin, 1982, p. 127-149.
19. Donadio JV Jr, Holley KE, Ferguson RH, Ilstrup DM: Treatment of diffuse proliferative lupus nephritis with prednisone and combined prednisone and cyclophosphamide. *N Engl J Med* 299: 1151-1155, 1978.
20. Steinberg AD, Steinberg SC. Long-term preservation of renal fucntion in patients with lupus nephritis receaiving treatment that includes cyclophosphamide *versus* those treated with prednisone only. *Arthritis Rheum* 34: 945-950, 1991.
21. Austin HA, Boumpas DT. Treatment of lupus nephritis. *Semin Nephrol* 16: 527-535, 1996.
22. Frutos MA. Nefritis lúpica: tratamientos para hoy y mañana. *Nefrología* 21: 4-5, 2001.
23. Boumpas DT, Austin HA, Vaughn EM, Klippel JH, Steinberg AD, Yarboro CH, Balow JE. Controlled trial of pulse methylpredisolone *versus* two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 340: 741-745, 1992.
24. Rivera F. López-Gómez JM. Pérez-García R. Spanish Registry of Glomerulonephritis. Clinicopathologic correlations of renal pathology in Spain. *Kidney Int* 66: 898-904, 2004.
25. Weening JJ. D'Agati VD. Schwartz MM. Seshan SV. Alpers CE. Appel GB. Balow JE. Bruijn JA. Cook T. Ferrario F. Fogo AB. Ginzler EM. Hebert L. Hill G. Hill P. Jennette JC. Kong NC. Lesavre P. Lockshin M. Looi LM. Makino H. Moura LA. Nagata M. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int* 65: 521-30, 2004.
26. Mittal B, Rennke H, Singh AK. The role of kidney biopsy in the management of lupus nephritis. *Curr Opin Nephrol Hypert* 14: 1-8, 2005.
27. Frutos MA, Cabello M, Valera A, Aranda P, González-Molina M, Martínez-González JM, Ramos B, Ruiz A, Martínez-González JL y López de Novales E.: Nefritis lúpica: Estudio clínico y evolución de 18 pacientes con insuficiencia renal. *Nefrología* 4: 205-210, 1984.
28. Esdaile JM, Joseph L, MacKenzie T, Kashgarian M, Hayslett JP. The pathogenesis and prognosis of lupus nephritis: information from repeat renal biopsy. *Sem Arthr Rheum* 23: 135-148, 1993.
29. Ponticelli C, Moroni G. Renal biopsy in lupus nephritis: what for, when and how often. *Nephrol Dial Transpl* 13: 2452-2454, 1998.
30. Austin HA III, Muenz LR, Joyce KM. Prognostic factors in lupus nephritis. Contributions of renal histological data. *Am J Med* 75: 382-391, 1983.
31. Schwartz MM, Lan SP, Bernstein J, Hill GS, Holley K, Lewis J. Irreproducibility of the activity and chronicity indices limits their utility in the management of lupus nephritis. Lupus Nephritis Collaborative Study Group. *Am J Kidney Dis* 21: 374-377, 1993.
32. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomized controlled trial. *Lancet* 361: 117-124, 2003.
33. Luño J. Efecto del tratamiento combinado con IECAs y ARAs sobre la proteinuria y función renal en pacientes con glomerulonefritis crónica. *Nefrología* 22 (Supl. 2): 41-43, 2002.
34. Dooley, MA, Hogan S, Jennette C, Falk R. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. *Kidney Int* 51: 1188-1995, 1997.
35. Barr RG, Seliger S, Appel G, Zuniga R, D'agati V, Salmon J, Radhakrishnan J. Prognosis in proliferative lupus nephritis: the role of socio-economic status and race/ethnicity. *Nephrol Dial. Transplant* 18: 2039-2046, 2003.
36. Balow JE, Austin HA. III. Maintenance Therapy for Lupus Nephritis - Something Old, Something New. *N Engl J Med* 350: 1044-1046, 2004.
37. Mok CC, Ying KY, Ng WL, Lee KW, To CH, Lau CS, Sing Wong RW: Long-term outcome of diffuse proliferative lupus glomerulonephritis treated with cyclophosphamide. *Am J Med* 119: 355.e26-355.e33, 2006.
38. Roman MJ, Shanker BA, Davis A, Lockshin MD, Sammaritano L, Simantov R, Crow MK, Schwartz JE, Paget SA, Devereux RB, Salmon JE. Prevalence and Correlates of Accelerated Atherosclerosis in Systemic Lupus Erythematosus. *N Engl J Med* 349: 2399-2406, 2003.
39. Park JC, Park YB, Jung SY, Chung IH, Choi KH, Lee SK. Risk of Ovarian Failure and Pregnancy Outcome in Patients With Lupus Nephritis Treated With Intravenous Cyclophosphamide Pulse Therapy. *Obst Gynecol Survey* 60: 148-150, 2005.
40. Kang I, Park SH. Infectious complications in SLE after immunosuppressive therapies. *Curr Opin Rheumatol* 15: 528-534, 2003.
41. Álvarez L, Gil CM, Jiménez del Cerro LA, Olivares J, Rivera F. Micofenolato mofetil en la nefritis lúpica. *Nefrología* 22: 24-32, 2002.

42. Moroni G, Greloni, GC, Ponticelli C. Late recurrence of lupus nephritis after long-term clinical remission. *Nephrol Dial Transplant* 16: 849-852, 2001.
43. Carlavilla A, Gutiérrez E, Ortuño T, Morales E, González E, Praga M. Relapse of lupus nephritis more than 10 years after complete remission. *Nephrol Dial Transplant* 20: 1994-1998, 2005.
44. Mok CC, Ying KY, Tang S y cols: Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. *Arthr Rheum* 50: 2559-2568, 2004.
45. Sidiropoulos PI, Kritikos HD, Boumpas DT. Lupus nephritis flares. *Lupus* 14: 49-52, 2005.
46. Houssiau FA, Vasconcelos C, D'Cruz D. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from the long term follow up of the Euro-Lupus Nephritis Trial. *Arthritis Rheum* 50: 3934-3940, 2004.
47. Frutos MA, González Molina M, Aranda P, Cabello M, Martín-Reyes G, Valera A, Ramos B, Ruiz A, López de Novales E. Ciclosporina en el tratamiento del lupus eritematoso sistémico grave. *Nefrología* 7: 396-400, 1987.
48. Mok, CC. Cyclophosphamide for Severe Lupus Nephritis: Where Are We Now? *Arthritis Rheum* 50: 3748-3750, 2004.
49. McCune WJ. Mycophenolate mofetil for lupus nephritis. *N Engl J Med* 353: 2282-2284, 2005.