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Malaga Study: 25 Year Background in Lupus Nephritis in South of Spain

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Abstract

Kidney disease has influenced the prognosis of patients with systemic lupus erythematosus (SLE). Fortunately better strategies and new immune-suppressants in the last decades have improved renal and survival prognosis. To study the patient and renal survival and prognostic factors in a cohort of 144 patients with severe lupus nephritis (LN) over a 25-year period at three Southeast Spain centres. We undertook a retrospective analysis of four groups related to time and kind of induction and maintenance treatment. Group A (1985-1990:24 monthly iv-cyclophosphamide [ivCyP]); Group B (1991-2000:6 monthly +18 quarterly ivCyP); Group C (2001-2004: fortnightly ivCyP) plus azathioprine [AZT] or mycophenolic acid [MA]; Group D (2005-2010: MA). The whole time of following was 124±86 m. In the first two years, a successful complete or partial response rate was experienced in 92 (77%) without intergroup differences. There was no difference between groups for lupus activity, renal function or proteinuria in repeated measures at 6, 18 and 24 months of following.

Overall patient survival by Kaplan Meier test at 5, 10 and 20 years was 92%, 87% and 80%, respectively. The Cox multivariate analysis confirmed that independent prognostic factors for death were older age at diagnosis (Hazard Ratio: 1.05), kidney survival (HR: 1.55) and having an infection (p=0.044). Similarly, overall kidney survival at 5, 10 and 20 years was 91.2%, 80.7% and 61.5%, respectively. The final prognosis factors were higher level baseline creatinine (HR 1.30) and reaching complete remission (HR 0.23). No significant intergroup differences were found concerning kidney and patient survival. Forty five of 115 responder patients (39%) during whole follow-up suffered one or more relapses. Patients maintained with AZA had higher risk to develop a flare. Treatment of severe LN with different strategies adapted to the evolution of knowledge with ivCF or MA were effective and safe, even with regimens that progressively reduce time and doses, leading to a real and hopeful patient and renal survival rate, without differences between groups.

Keywords Lupus nephritis; Cyclophosphamide; Mycophenolic acid; Azathioprine; Chronic renal failure; Lupus relapses

Introduction

Lupus nephritis (LN) is a prevalent and important problem in systemic lupus erythematosus (SLE), occurring in up to 40-75% [1] and accounting for most of the mortality and morbidity among these patients [1,2]. Until about 30-40 years ago, the prognosis for patients with LN was very poor, but it has improved noticeably with new treatment strategies [3,4]. Treatment with CF has been considered the first option by different groups, [5-8] including ours [9]. Since its toxicity is related with the total accumulated dose, [5] the tendency has been towards dose reduction strategies, keeping its efficacy but getting its side-efects down [6,7]. At the end of the 1990s, first reports appeared about the use of mofetil mycophenolate (MMF) in refractory cases of LN [10-12]. Nowadays, indication for MMF as the first choice as induction and maintenance therapy is endorsed enough [13-18]. The present study aimed to evaluate the experience of a southeast of Spain multidisciplinary group with a large series of patients with severe LN treated with different schedule of induction and maintenance immunosuppressive therapy over a 25-year period.

Patients and Methods

Since 1985, rheumatologists, internists and nephrologists from three Southeast Spain reference hospitals started attending lupus patients classified in accordance with ACR criteria [19]. We describe our cohort of patients retrospectively studied. Kidney biopsies were all studied by the same expert nephro-pathologist according to the relevant classification for each period [20].

Treatment schedule

Between 1985 and 1990, patients with severe LN were given ivCF 0.75 g/m^2, monthly, for 24 months (Group A, n=36). Since 1991, this schedule was changed to quarterly pulses since 6th to 24th month (Group B, n=61)[5]. With effect from 2000, the regimen for induction was CF 500 mg fortnightly pulses for three months and for maintenance, oral azathioprine (AZT) 2 mg/kg or MMF (500-1000 mg,

b.d.) for 36 months (Group C, n=21). From 2004 we started considering MA as induction (MMF, 1000-1500 mg, b.d., or MA-EC, 720-1080 mg, b.d., progressively for 24 weeks), and maintenance therapy (MMF, 1000 mg b.d., or MA-EC, 720 mg, b.d. for 36-60 months) (Group D, n=26). The steroid regimen was as follows: Three pulses consecutively daily of 500 mg of 6-methyl-prednisolone when acute renal failure, severe systemic involvement of SLE, or severe nephrotic syndrome was present. Then, up until 2000, the patients received prednisone 1 mg/kg/d the first month (maximum, 60 mg/d), and progressively tapering until 5 mg/d at the beginning of maintenance treatment. From 2001, the starting dose was 30 mg/d and the same tapering that previous.

Outcome variables definitions

Kidney survival time for start of immune-supresssive treatment to doubling of initial serum creatinine (mg/dl) or necessity of renal replacement therapy for, at least, two months [21]. Complete response (CR): reduction in proteinuria (g/24 h urine) to at least 500 mg/d, absence of activity in the sediment and normalization or stabilization of the serum creatinine (± 25% of baseline level). Partial response (PR): reduction in proteinuria by at least 50% compared with baseline, absence of activity in the sediment and normalization or stabilization of the creatinine. No response (NR): absence of complete or partial remission. Relapse: presence of a) or b) ± c) after finishing induction therapy. a) Proteinuric-Nephrotic relapse: reappearance of proteinuria at over 0.5 g/d, if there had been complete response or an increase in proteinuria (>50% from baseline) if the response had been partial, with or without mild active sediment and/or mild increase in creatinine; b) nephritic relapse: reappearance of active sediment (>5 red cells and/or >5 leukocytes per high power field) and a habitual increase in creatinine more than 25% above baseline, with or without proteinuria in the non-nephrotic range; c) presence of extra-renal lupus activity parameters. Side effects: gastrointestinal (nausea, vomiting or diarrhoea), infections, osteoporosis, early amenorrhea (menopause before forties) and tumours.

	Average	Range	SD	CI 95%
Baseline creatinine	1.38	0.40-9.70	1.14	1.19-1.57
24 h proteinuria	4.73	0-16	3.50	4.15-5.31
Age	30.48	11-68	11.32	28.60-32.35
Activity index	9.02	0-18	3.53	8.28-9.77
Chronicity index	0.94	0-4	1.06	0.72-1.17
C3	57.58	6-122	24.90	53.43-61.73
C4	11.42	2-115	11.22	9.56-13.29
Haemoglobin	11.08	6-16	2.13	10.72-11.44
Leuckocytes	5425.80	2100-11700	2193.05	5037-5814
Platelets	219808	245-523000	106642	199170-240446
Anti-DNA	193.57	0-385	33.37	127-259
ANA	279.34	2560	265.77	231-326

Table 1: Baseline patient characteristics (at the moment of the biopsy).

Statistical study

Study patients variables were included in SSPS.15.0 database. Mean and standard deviation and relative frequencies were used for descriptive statistics since the data were normal distributed. One-way ANOVA and the Chi square were used to compare quantitative and qualitative variables, respectively. Comparison of the results obtained in the four treatment groups was done by repeated measures ANOVA, with the various serum and urine analytical measures as dependent variable, time (0, 6, 18 and 24 months) as being the intragroup factor and the immunosuppressive treatment period as intergroup factor. Survival functions were calculated with Kaplan-Meier analysis and Log Rank test with alpha error <0.05 in two-tailed tests. The models resulting from the multivariate analyses were done by Cox regression (hazard ratios/HR) or logistic regression (odds ratios/OR), with the Wald statistic for stepwise introduction of data, considering an input level of significance of 0.10 and output of 0.20.

Results

The baseline characteristics of the patients in the four groups are shown in Table 1. The study included 144 patients (116 women). The mean follow-up period was 124.82 months, SD 86.20. Group A included 35 (92.2%) class IV and 1 class V nephritis, group B 48 (87.5%) class IV and 8 class V nephritis, group C 12 (63.2%) class IV and 7 class V nephritis, and group D 9 (39%) class IV and 14 class V nephritis. The clinical forms of presentation detected were: proteinuria in 139 patients (97% of the cases), of which it was nephrotic in 78 (54%); 104 (72%) had active sediment; 47 (33%) manifested with serum creatinine >1.3 mg/dl.Hypertension at the onset of the disease was found in 75 patients (51.4%). An initial evaluation of the study groups shows similar values for gender, activity and chronicity pathological index (CI). Patients in group A started with higher serum creatinine levels (2.08 ± 1.68 mg/dl) compared with the other groups (B: 0.82 ± 0.48, C: 1.10 ± 0.96, D: 0.93 ± 0.45 mg/dl), p<0.001. Proteinuria was also higher in group A (6.11 ± 4 g/d) than the other groups (B: 4.5 ± 3.4, C: 4.5 ± 2.9, D: 4.7± 3.5 g/d), p=0.030. The presence of hypertension was more common in group A patients than those in groups B, C and D, (p=0.057).

However, the percentage of patients treated with ACE inhibitors or ARA II did reach a significant difference (p=0.001), being greater in the most recently treated patients 28% group A, 39% B, 62% C, 77% D).

The overall patient survival of the whole group in Kaplan Meier analysis at 5, 10, 15 and 20 years was 92%, 87%, 80% and 80%, respectively. There were 18 deaths. The mean age at death was 41.6 ± 11.6 years. Cause of it was cardiovascular in 10 patients, sepsis-multiorgan failure in three, traffic accident in one, haemorrhagic stroke in one and three patients died for unknown reason. The multivariate Cox proportional hazards analysis confirmed that the independent prognostic factors of death were age at diagnosis of the nephritis (p=0.023, Hazard Ratio HR1.05, 95% CI 1.01-1.10), and kidney survival (p=0.046, HR 1.55, 95%CI 1.01-2.55) (table 2). No difference between four treatment groups was found (Log-rank test: $\chi^2 = 4.009$, p=0.252) (Figure 1.A).

Kidney survival in Kaplan Meier analysis at 5, 10, 15 and 20 years were 91.2%, 80.7%, 67.1% and 61.5%, respectively. The final model of multivariate Cox proportional hazards analysis retained the prognostic variables, baseline serum creatinine (p=0.022, HR 1.30, 95% CI 1.10-1.61) and complete remission (p=0.004, HR 0.23, 95% CI

0.08-0.63) (Table 3). Once more, no difference between four treatment groups was noted (Figure 1.B).

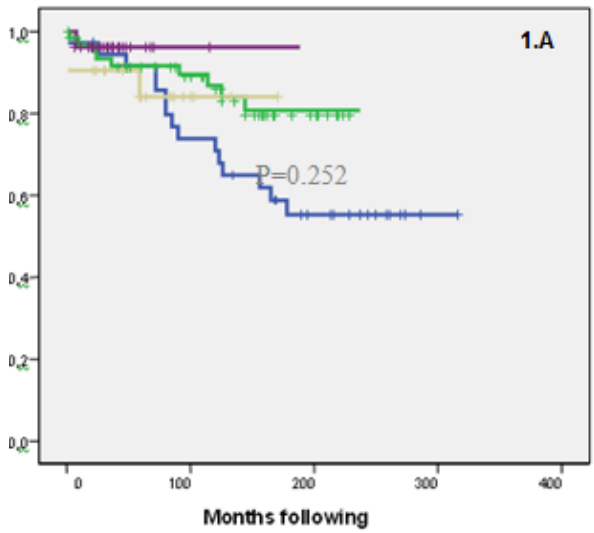
Variable	Univariate p, HR (CI 95%)	Multivariate p, HR (CI 95%)
Age	p=0.019, HR 1.05 (1.01-1.09)	p=0.023, HR 1.05 (1.01-1.10)
Gender	p=0.809, HR 1.15 (0.37-3.48)	-
Nephritis type	p=0.542	-
III vs IV	p=0.554, HR 1.58 (0.34-7.23)	-
III vs V	p=0.278, HR 2.72 (0.44-16.67)	-
V vs IV	p=0.422, HR 0.58 (0.15-2.18)	-
Activity index	p=0.730, HR 0.97 (0.82-1.14)	-
Chronicity index	p=0.561, HR 1.15 (0.70-1.90)	-
Baseline creatinine	p=0.834, HR 1.03 (0.74-1.43)	-
Baseline proteinuria	p=0.572, HR 1.04 (0.91-1.17)	-
Hypertension	p=0.197, HR 1.68 (0.74-3.72)	-
6 month remission	p=0.301, HR 1.73 (0.61-4.9)	-
24 m creatinine	p=0.344, HR 1.62 (0.59-4.36)	-
24 m proetinuria	p=0.515, HR 1.04 (0.91-1.19)	-
24 m remission	p=0.441, HR 0.62 (0.19-2.07)	-
Relapse	p=0.590. HR 1.29 (0.49-3.35)	-
Kidney survival	p=0.057, HR 2.48 (0.97-6.31)	p=0.046, HR 1.55 (1.01-2.55)
Group of treatment	p=0.288	-
A vs B	p=0.659, HR 1.28 (0.40-4.00)	-
A vs C	p=0.139, HR 2.14 (0.69-14.28)	-
A vs D	p=0.113, HR 4.43 (0.70-27.80)	-
Infections (24 m)	p=0.044, HR 1.27 (1.00-1.58)	-

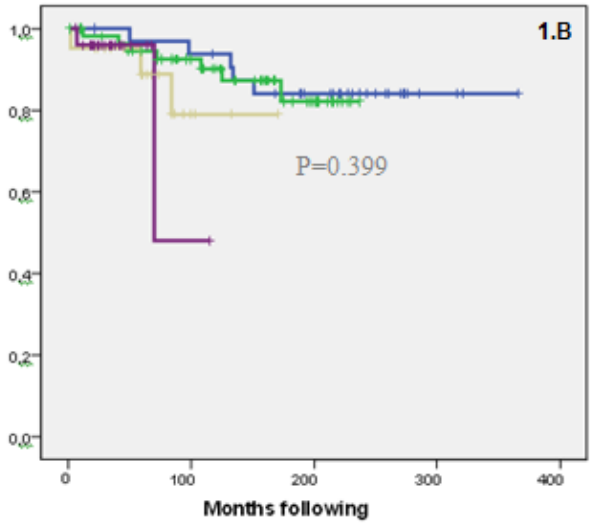
Table 2: Patient survival, Cox univariate and multivariate analysis. PR: partial remission; CR: complete remission; NR: no remission; HR: Hazard ratio; CI: confidence interval

Variable	Univariate p, HR (CI 95%)	Multivariate p, HR (CI 95%)
Age	p=0.759, HR 1.00 (0.97-1.04)	-
Gender	p=0.830, HR 0.90 (0.34-1.19)	-
Nephritis type	p=0.438	-
III vs IV	p=0.666, HR 1.24 (0.46-3.32)	-
III vs V	p=0.328, HR 0.34 (0.04-2.95)	-
V vs IV	p=0.212, HR 3.65 (0.17-27.9)	-
Activity index	p=0.003, HR 1.35 (1.10-1.65)	-
Chronicity index	p=0.002, HR 1.92 (1.26-2.90)	-
Baseline creatinine	p=0.001, HR 1.31 (1.12-1.52)	p=0.022, HR 1.30 (0.08-0.63)
Baseline proteinuria	p=0.359, HR 1.05 (0.95-1.16)	-
Hypertension	p=0.197, HR 1.68 (0.74-3.72)	-
6 month remission	p=0.626, HR 0.80 (0.33-1.92)	-
24 m remission	p=0.065	p= 0.016
No R vs PR	p=0.646, HR 0.75 (0.22-2.51)	p=0.136, HR 0.29 (0.06-1.46)
NR vs CR	p=0.023, HR 0.329 (0.12-0.85)	p=0.04, HR 0.23 (0.08-0.63)
Relapse	p=0.294, HR 1.52 (0.69-3.29)	p= 0.116, HR2.16 (0.83-5.63)
Baseline platelets	p=0.80, HR 1.00 (1.00-1.00)	-
Baseline haemoglobin	p=0.80, HR 0.97 (0.80-1.18)	-
Baseline leuckocytes	p=0.74, HR 1.00 (1.00-1.00)	-
Infection	p=0.16, HR 1.14 (0.94-1.37)	-
Group of treatment	p=0.45	p= 0.506, HR 1.30 (1.03-1.61)
A vs B	p=0.13, HR 0.53 (0.23-0.12)	p= 0.138, HR 0.47 (0.17-1.27)
A vs C	p=0.75, HR 0.80 (0.22-0.29)	p=0.48, HR 0.46 (0.54-4.03)
A vs D	p=0.38, HR 0.39 (0.05-3.20)	p=0.978, HR 0.00 (0.00)

Table 3: Kidney survival. Cox univariate and Cox multivariate analysis.

The repeated measures analysis showed a significant improve in levels of serum creatinine, haemoglobin, platelets and proteinuria in the overall group over time ($p<0.001$) and to normalize the serum parameters of SLE immunological activity (C3 and anti-DNAn) significantly ($p<0.001$) in the first 6 months, after which they were stable (Figure 2). No significance differences between groups were observed.





n/month	60	120	180	240
A	32	30	26	13
B	50	34	15	0
C	13	2	0	0
D	4	0	0	0

GROUP OR TIME OF TREATMENT
A
B
C
D

n/mes	12	60	120	180	240
A	35	31	25	17	9
B	55	46	30	10	0
C	19	11	2	0	0
D	23	4	0	0	0

Figure 1: Kaplan Meier survival curves. **1.A:** patient survival. **1.B:** kidney survival (Tables: patients on following).

At 6 months, we got available data of 130 patients, whom 87 had attained criteria of CR (39.2%), or PR (27.7%). In the logistic regression multivariate model only baseline proteinuria ($p=0.034$, OR 1.16, 95% CI 1.01-1.34) remained as predictive factor of CR or PR. At 24 months, we got available data of 120 patients, whom 92 had attained criteria of CR (62.5%) or PR (14.2%). In the multivariate analysis, elevated baseline creatinine was the only variable remaining in the final model as an independent predictive factor of no response ($p=0.001$, OR 1.33, 95% CI 1.12-1.57). The main adverse events from less to most important, included gastrointestinal, experienced by 7 of the 26 patients in group D. An infectious was seen in 56 patients (39%). Urinary tract infections were the most common (33 patients, 59%), followed by cutaneous herpes zoster (13 patients, 23%) and pneumonia (5 patients, 9%). One patient had laryngeal tuberculosis, and another, peritonitis secondary to complicated acute pancreatitis. Other infections included oro-pharyngeal or genital candidiasis and herpes simplex. Most resolved without squeal, except for two patients who had septic multi organ failure (peritonitis and pneumonia due to CMV) of the four malignant neoplasms that developed (2.9%), one was of the breast, one endometrial, one non-Hodgkin lymphoma and one colon carcinoma.

None has yet resulted in death. The most severe bone alterations in the series were avascular necrosis of the femoral head (16 patients), all diagnosed clinically and requiring prosthetic replacement. One patient had clinically evident vertebral fracture compression. The only adverse event with difference between groups was amenorrhea, qualified as early menopause, that was noted in 10 women (37%) in group A, 9 (19.6%) in group B, and none in groups C and D (χ^2 =16,86, $p=0.001$). Data for flares were obtained for 115 patients who had remission during the following. Forty-five (39%) had renal relapse. Twenty-eight had one single flare, nine had two flares, six had three, one had five and another had seven. The flare presentation form was nephrotic, in 30 cases (66.6%) and nephritic in 9 cases (20%). At 2 and 5 years respectively, the mean relapse-free time of the whole sample was 66 and 60%, respectively: 90 and 70% for group A, 73 and 67% for group B, 46% for group C and 58% for group D (LR 9.23, $p=0.026$, Figure 3). In the multivariate Cox analysis, the variable treatment group confirmed that group C had a higher risk of relapse than group A ($p=0.020$, HR 2.66, CI 95% 1.15-6.10). Group C-AZT seems to be the responsible of this difference ($p=0.043$, HR 3.25, 95% CI 1.04-10.22) more than group C-MMF ($p=0.069$).

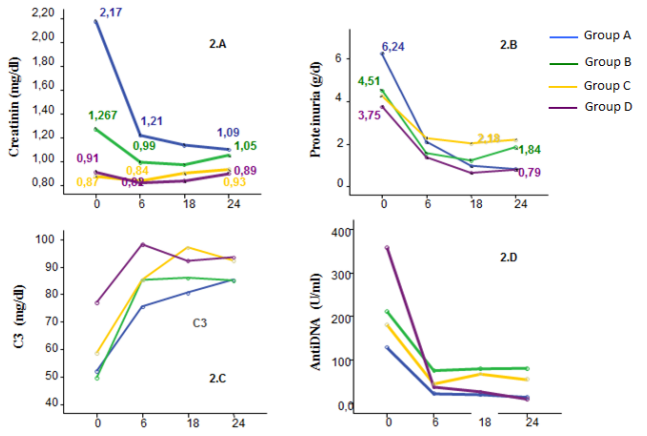


Figure 2: ANOVA repeated measures from 0 to 24 months. **2.A:** creatinine; **2.B:** proteinuria; **2.C:** C3; **2.D:** antiDNA.

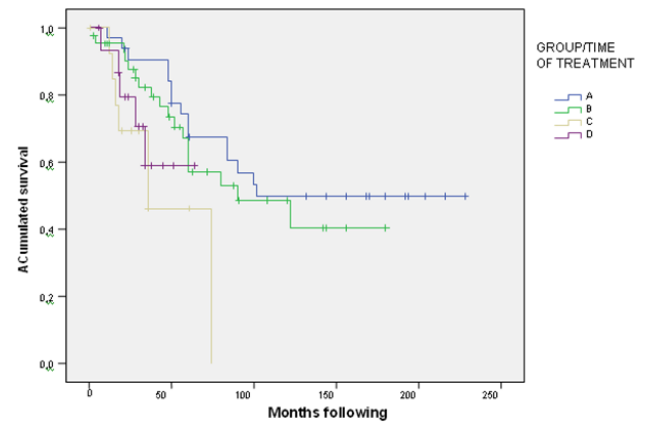


Figure 3: Relapses-free time, Kaplan Meier curve.

Discussion

Our study includes a large cohort of patients with LN over a long period of follow up that received different immune-suppressive treatments but, because of this long period, also may have been treated of different way from other point of view, not just under immunosuppressive one [4,22]. However, a similar patients and kidney survival was observed between these different therapeutics regimens or periods of time.

The mean baseline creatinine was 1.38 mg/dl even though no patient was excluded due to this, unlike in other studies [23,24]. The greater creatinine, proteinuria and hypertension at the time of the biopsy in group A may be related with a later diagnosis than in other groups, as concerning a better knowledge of lupus patients now than before, although time between beginning of symptoms and diagnostic are no analysed by the characteristic of the study. Fiehn [4] and Bono, et al. [25] found similar data when also comparing treatment decades, contrary to Croca [26]. Moreover, in our study, patients preventing from group A belonged to Nephrology -patients whom lupus diagnosis was made by a nephrologist, and suffered from renal failure at the time of diagnosis more than patients from Internal Medicine or Rheumatology ($p<0.001$, data not shown), who are diagnosed from lupus, and, after a period of time, suffer from nephritis.

The progressively increasing prescription of ACE inhibitors or ARA 2 as we approached the current period is in agreement with the tendency to use these drugs as anti proteinuric agents and not just for the treatment of hypertension [27].

Low values in the CI can be explained because all patients were recently diagnosed and treated in their first episode. This circumstance may have influenced positively the good response to treatment in the whole group.

Patient survival was very satisfactory for the overall series, within the range aimed for other series, as the main aetiologies of death, cardiovascular and infectious [1,25,28-30]. In our multivariate analysis, each year of age increased by 5% the probability of death, just as doubling the serum creatinine was associated with a 55% higher probability, as also seen by many others [1,30-31]. Nor did the presence or degree of remission have an influence in our univariate or multivariate tests, unlike the study of Korbet et al. and others [31-32]. This may be influenced by the difference in the definition of remission. Group of treatment neither influenced in patient survival, unlike the studies by Bono [25] and Croca [26], in whose older cohorts, survival was significantly lower. Bono´s time-schedules and Coca´s statistical tests were different from ours.

Our rate for kidney survival is also similar in the whole cohort and to those of other series with the same treatment era [33,34]. Fiehn et al. [4] found a better kidney survival in the 1990s than before, but we should recall the low number of patients included at that time (n=15), the different outcome measure and the different time from first detection of proteinuria until kidney biopsy in theirs groups. Factors that influenced for the development of chronic renal failure (CRF) in our cohort were baseline creatinine and reaching or maintaining the response at 2 years. The greater significance seemed to be for complete remission, though partial remission and chronicity index in the subgroup of patients with complete information also seemed to have a beneficial influence on kidney survival, as also seen, by other authors-studies [30,35-37], by Chenn, et al. [31] Renal flares, however, did not influence for kidney survival, finding also reported by Illei et al in a cohort of 145 patients followed for a long time [38,39]. We assume this lack of relation to the earliness in the diagnosis and treatment of these flares, and do not reject capacity of relapses to induce kidney damage.

The influence of an early response to therapy on kidney survival in LN patients is very-well known [39-40], though in our series just 2 years response reached statistical significance for this end-point. However, a majority of our patients responded early at 6 months, with each gram of baseline proteinuria representing a 15% risk of no response, like Sisó el at al. [28] and Touma Z, et al. [41], who show time to recovery from proteinuria can be slow. Treatment did not result as risk factor in unit multivariate analysis. Others groups with response rates similar to ours, have studied similar schedules of treatment [12,14,23-24] and, not found differences between groups neither, excepting Ginzler, et al. [24].

The incidence of renal flares in our series was in the range of published [13,33-34,40,42]. In accordance with some reports and unlike others, no serological or clinical baseline date was related to suffer from a relapse. Just the variable treatment group was shown to be predictive of flare, in favour of use of high-dose cyclophosphamide versus the quarterly regimen of group C. ELNT6 was unable to

corroborate this, but we should bear in mind the follow-up period of our series and different comparative groups between the published papers. It is also notable that on many occasions division between induction and maintenance treatment is difficult when comparing different protocols. That is, comparison between our group C, with an induction period of 3 months, and rest of groups, of 6 months, sometimes leads to a systematic error that is hard to interpret. We carried out a subgroup analysis, dividing group C in two categories according to AZT or MMF maintenance treatment. We observed that the difference between C and A groups for suffer from flares was confirmed in AZT-C-group (p=0.018) but not in MMF-C-group (p=0.062), in agree with ALMS24. Could it suggest that after induction with low doses of CF is better using MMF than AZT for maintenance? MAINTAIN study reported similar results but without statistical significance.

The incidence of premature menopause in groups with elevated dose of cyclophosphamide deserved to be mentioned, so current schedule go after less dose of cyclophosphamide to avoid this side effects.

The limitations of this study include those implicit to any retrospective work. Any comparison between the groups should consider that group B had twice number of patients than the other arms and minor follow-up in the more recent groups. Moreover, nephritis from group A and B seemed to be more severe than other ones.

To finish, not just treatment but period of time with 25 years between the first and the last group may definitely influence in the course of nephritis. Because of that, we prefer to speak about period of time under different schedules of treatment which combine different drug with different adjuvant factors.

Conclusion

Our experience confirm that induction treatment of severe LN with different immune-suppression with ivCF or MMF and maintenance with AZT or MMF, is effective and safe, leading to a real and hopeful patient and kidney survival rate. However, the doses of treatment with ivCF and the time for withdrawal of maintain treatment is still in discussion. In our patients, low dose of ivCF plus AZA seems to be less effective to avoid renal flares. Older age and renal chronic failure at diagnosis were predictors of mortality. The side effects we have observed as consequence of immunosuppressive treatment can be described as milder inside benefit-risk thought. None of tested treatment seems to contribute by different grade to prevalence of Infections. Ovarian failure seems to be related to elevated doses of CF treatment.

The main causes of death were cardiovascular and infection. Serum creatinine and chronicity index at baseline and reaching renal response at 24th month, were excellent prognostic factor of renal survival in this study. By now, we diagnose milder LN than previous rears, with better renal function, less proteinuria and less prevalence of hypertension. We attribute it to a prompt diagnostics.

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