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Long-term efficacy and safety of the Lupus-Cruces Nephritis protocol: a propensity score study of the Lupus-Cruces and Lupus-Bordeaux cohorts

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ABSTRACT

Objective To assess the efficacy and toxicity of the Lupus-Cruces Nephritis (LCN) protocol compared with standard of care (SOC) with cyclophosphamide (CYC) or mycophenolate in patients with lupus nephritis (LN) during an extended follow-up time up to 10 years.

Methods Patients with biopsy-proven class III, IV or V LN treated with LCN were compared with SOC. Patients in the LCN were treated with a CYC plus repeated methylprednisolone pulse-based regimen. The achievement of complete renal response (CRR) and the progression to chronic kidney disease (CKD) were the two main outcomes. Glucocorticoid (GC)-related toxicity, major infections and damage accrual were also analysed. A propensity score (PS)-adjusted multivariate analysis was used to overcome the confounding-by-indication bias.

Results 147 patients were included in this study (47 LCN and 100 SOC). CRR at 12 months was 85% vs 44%, respectively (p<0.001). Eventually, 96% patients in the LCN group achieved CRR vs 74% patients in the SOC (p=0.002). In the multivariate PS-adjusted Cox model, LCN patients were more likely to eventually achieve CRR (PS-adjusted HR 3.5, 95% CI 2.2 to 5.5, p<0.001). The risk of progression to CKD was lower in LCN patients (PS-adjusted HR 0.3, 95% CI 0.11 to 0.82, p=0.019). The risks of GC-induced toxicity, renal or GC-related damage accrual and major infections were also lower in the LCN group: adjusted HR 0.09, 95% CI 0.02 to 0.39; PS-adjusted HR 0.14, 95% CI 0.04 to 0.4; PS-adjusted HR 0.2, 95% CI 0.046 to 0.95; respectively.

Conclusions This study confirms the LCN protocol as an effective and safe, in addition to widely available and affordable, regimen for the induction therapy of LN.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Lupus nephritis (LN) has a strong prognostic impact in patients with SLE, with a significant number of patients not achieving complete renal response (CRR) and experiencing progression to chronic kidney disease (CKD) as well as glucocorticoid (GC)-related toxicity.

⇒ The standard of care (SOC) therapy for LN is based on cyclophosphamide (CYC) or mycophenolate (MMF), with recent calls for the earlier use of new and more costly drugs, which are not available for many patients in a worldwide setting.

WHAT THIS STUDY ADDS

⇒ The Lupus-Cruces Nephritis (LCN) protocol, based on CYC and repeated methylprednisolone pulses, resulted in higher CRR, lower CKD rates and damage than the CYC or MMF-based SOC.

⇒ In addition, the GC load and GC-related toxicity were significantly reduced.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The LCN protocol is effective and safe, in addition to widely available and affordable.

⇒ The wider implementation of the LCN protocol could help improve the long-term prognosis of LN while reducing the impact on treatment-derived costs.

INTRODUCTION

Lupus nephritis (LN) is the most frequent visceral involvement in SLE, exerting a strong prognostic impact on the course of the disease.[1] Around 40% patients with SLE can eventually develop LN, many of them during the initial phases of lupus.[1] Even in recent years, patients with LN are at high risk of chronic and end-stage kidney disease (CKD and ESKD, respectively) needing dialysis and/or renal transplantation.[2 3] Complete renal response (CRR) at 12 months has been consistently found to protect from progression to CKD and ESKD.[4]

Therapy of class III, IV and V LN has been traditionally based on high-dose glucocorticoids (GC) combined with

immunosuppressive therapy, mainly cyclophosphamide (CYC) or mycophenolate (MMF), which constitute the current standard of care (SOC).[3 5] Recent guidelines consider decreasing the initial prednisone dose and using more rapid tapering schemes.[3 6] However, the universal use of methylprednisolone pulses (MP) and the strict, fixed and quick tapering of prednisone to 5 mg/day in less than 6 months are considered as an option rather than being strongly recommended.[3 5 6]

The Autoimmune Diseases Unit at the Department of Internal Medicine, Hospital Universitario Cruces (EAS) was established in 2001.[7] Our therapeutic scheme for LN was gradually amended after 2004, with the progressively extended use of MP followed by the reduction in oral GC dose. In 2006, we elaborated a protocol, modified from the Eurolupus Nephritis protocol,[8] which included the repeated administration of MP with each 2 weekly intravenous dose of 500 mg of CYC, establishing a maximum dose of oral prednisone of 30 mg/day (irrespective of patients' weight) on starting induction therapy, and achieving a fixed rapid reduction to 5 mg/day in 12–14 weeks. In 2014, we first published our results with this therapeutic scheme, the Lupus-Cruces Nephritis (LCN) protocol, comparing a group of 15 so-treated patients with 30 historic controls.[9] The good data encouraged us to implement this scheme, further reducing the load of oral prednisone by using initial doses of 20–30 mg/day and a fixed tapering time of 12 weeks to a dose of 5 mg/day. In 2017, we published an observational study comparing the clinical course of 29 patients with biopsy-proven LN from the Lupus-Cruces cohort with 44 patients from the Lupus-Bordeaux cohort.[10] This study confirmed the better results of the Lupus-Cruces cohort and identified the repeated administration of MP as an independent predictor of CRR.[10] In 2021, the series was expanded to 93 patients, allowing us to compare 3 different therapeutic arms: the LCN protocol, the Eurolupus CYC-based and the MMF-based regimens,[11] showing the superiority of the LCN protocol over the other two.

All the above studies used CRR at 12 months as the main outcome variable. Despite the good predictive prognostic value of this outcome regarding the progression to CKD,[12] the long-term results of the LCN protocol have not been investigated. Now, taking advantage of the expansion of our prospective cohort, both in number of patients and follow-up time, we aim to assess the efficacy and toxicity of the LCN protocol compared with SOC within an extended follow-up of up to 10 years.

PATIENTS AND METHODS

Study design and patients

This is an observational comparative study using routine clinical care data. Patients with biopsy-proven LN from the longitudinal Lupus Cruces (Cruces-EAS, n=62) and Lupus Bordeaux (BDX, n=43) cohorts were merged with patients from the historic Lupus Cruces cohort (Cruces-historic, n=42), that is, those diagnosed with SLE in our Department up to year 2001.[7 9] All eligible patients fulfilled the American College of Rheumatology or the Systemic Lupus International Collaborating Clinics (SLICC) criteria for the classification of SLE,[13 14] had class III, IV or V LN confirmed by renal biopsy[15] and had a follow-up of at least 12 months and up to 10 years. Patients with both first or recurring episodes of LN were included.

The LCN treatment protocol

The LCN protocol is shown in figure 1. All patients receive three initial consecutive intravenous MP of 250–500 mg. Then, patients receive iv CYC 500 mg/2 weeks, for a total number of 6 (up to 9 according to clinical response). MP 125–250 mg is given just before each dose of CYC. After 2020, patients with class V LN have also been treated with the LCN protocol, with the difference that a reduced number of CYC-MP doses, 3 or 6, were given according to clinical response.

After the three initial MP, oral prednisone is started at 20 mg/day, with a fixed rapid tapering to 5 mg/day in a maximum time of 12 weeks (20 mg/day×2 weeks, 15 mg/d×2 weeks, 10 mg/day x4 weeks, 7.5 mg/day×4 weeks, then 5 mg/day). In exceptionally severe cases, the initial dose can be increased to 30 mg/day for 2 weeks, and thus the time to 5 mg/day can be expanded to 14 weeks. After that, the reduction to ≤2.5 mg/day is gradually accomplished according to the clinical course of each patient. In no case, the dose of prednisone for maintenance therapy is >5 mg/day. Additional MP can be given in cases of insufficient control of renal and/or extrarenal activity.

After the induction phase is completed, either azathioprine or MMF is used as maintenance immunosuppressive therapy, azathioprine being the first option for white patients achieving early CRR, according to the results of the MAINTAIN trial.[16] The prescription of ACE inhibitors or angiotensin receptor blockers and vitamin D is dependent on the degree of proteinuria and serum 25 (OH) vitamin D levels, respectively. All patients receive baseline therapy with HCQ 200 mg/day.

Under certain circumstances, rituximab, belimumab and/or calcineurin inhibitors (CNI) can also be used. Rituximab is added to the initial CYC-MP therapy in patients presenting with life-threatening disease, such as concomitant myocarditis or pneumonitis, or in patients with worsening renal parameters within the first 3 months. Belimumab and/or CNI are added in patients in whom extrarenal symptoms are not well controlled on reducing the dose of prednisone (belimumab) or in whom the rate of reduction of proteinuria does not progress towards CRR after 3–6 months of therapy (CNI and/or belimumab, according to the degree of proteinuria and extrarenal activity).

SOC treatment schemes

The different schemes for the SOC are shown in figure 2. Patients from the BDX cohort (n=43), from the Cruces-EAS cohort not receiving the LCN protocol (class II/IV LN previous to 2006 or class V LN previous to

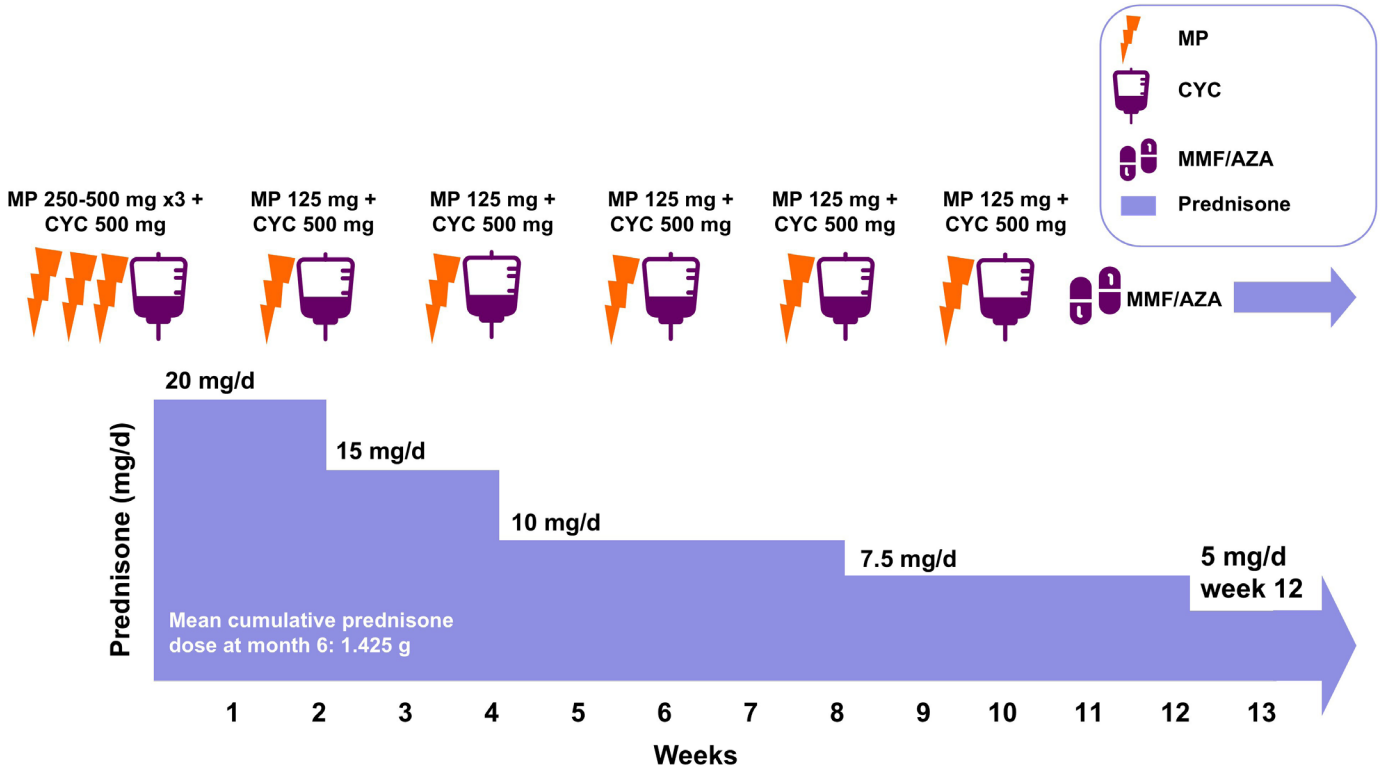

Figure 1 The LCN protocol. Indications for additional therapy (see text): Rituximab is added early in patients presenting with life-threatening disease or in patients with worsening renal parameters within the first 3 months. Belimumab and/or mepacrine are added in patients in whom extra-renal symptoms are not well controlled on reducing prednisone dose. Belimumab and/or CNI if the rate of reduction of proteinuria does not progress towards CRR after 6 months of therapy (belimumab and/or CNI, according to the degree of proteinuria and extrarenal activity). MP and CYC can also be extended (three more doses) in case of improvement after six doses but yet insufficient response. AZA, azathioprine; CNI, calcineurin inhibitors; CRR, complete renal response; CYC, cyclophosphamide; LCN, Lupus-Cruces Nephritis; MMF, mycophenolate; MP, methyl-prednisolone pulses.

2020, n=15) and from the Cruces-historic cohort (n=42) were grouped as the SOC group. Patients from the non-LCN-Cruces-EAS and BDX groups were treated either with MMF at a maximum dose of 1000 mg/12 hours, preceded by 3 MP (250–1000 g each) depending on the specific site protocol and disease severity, or with the Eurolupus intravenous CYC 500 mg/2 weeks regimen[8] preceded by 3 MP (usually 250–1000 mg each depending on disease status and site). Prednisone starting doses and tapering schemes depended on the site, with patients from the non LCN-Cruces-EAS cohort receiving initial doses ≤30 mg/day and patients from BDX 0.5 mg/kg/day. Those patients from the Cruces-historic cohort with class III/IV LN were treated with a high-dose CYC-based scheme,[8] with monthly intravenous CYC (1 g/m^2) for 6 months, followed by the same dose every 3 months for variable periods of time, up to 2 years. Prednisone was given at high doses (1 mg/kg/day) with variable duration and tapering schemes according to the clinical course of the patients. MP was given in selected patients. Likewise, HCQ and antiproteinuric drugs were not used as per protocol. Patients with class V LN were treated with combinations of prednisone and immunosuppressive drugs (azathioprine or MMF). Maintenance therapy included azathioprine or MMF, although five patients given long courses of CYC did not receive any additional maintenance immunosuppressive therapy. Seven patients in the Cruces-historic cohort received induction therapy with GC and azathioprine and one with GC only.

Baseline variables

We compared the following baseline variables in the two treatment groups (LCN and SOC): age, gender, race, smoking, hypertension, diabetes, positivity of anti-dsDNA, anti-Ro, anti-La, anti-RNP, anti-Sm and antiphospholipid antibodies, histological class of LN, first episode of LN (vs relapse), 24 hours proteinuria, as estimated by the protein/creatinine (Pr/Cr) ratio (g/g) in the first morning urine sample, serum creatinine and albumin levels (in mg/dL).

The following therapeutic variables were also compared between the two groups: initial prednisone dose during induction therapy, average daily prednisone dose by 6 months, number of weeks from the initiation of induction therapy until reaching a dose of 5 mg/day of prednisone, proportion of patients treated with MP, number of MP per patient, cumulative MP dose, proportion of patients treated with HCQ, HCQ daily dose, time of treatment with HCQ in 6 months (weeks) and proportion of patients treated with azathioprine, MMF, antiproteinuric drugs (ACE inhibitors/angiotensin receptor blockers) and vitamin D within 6 months.

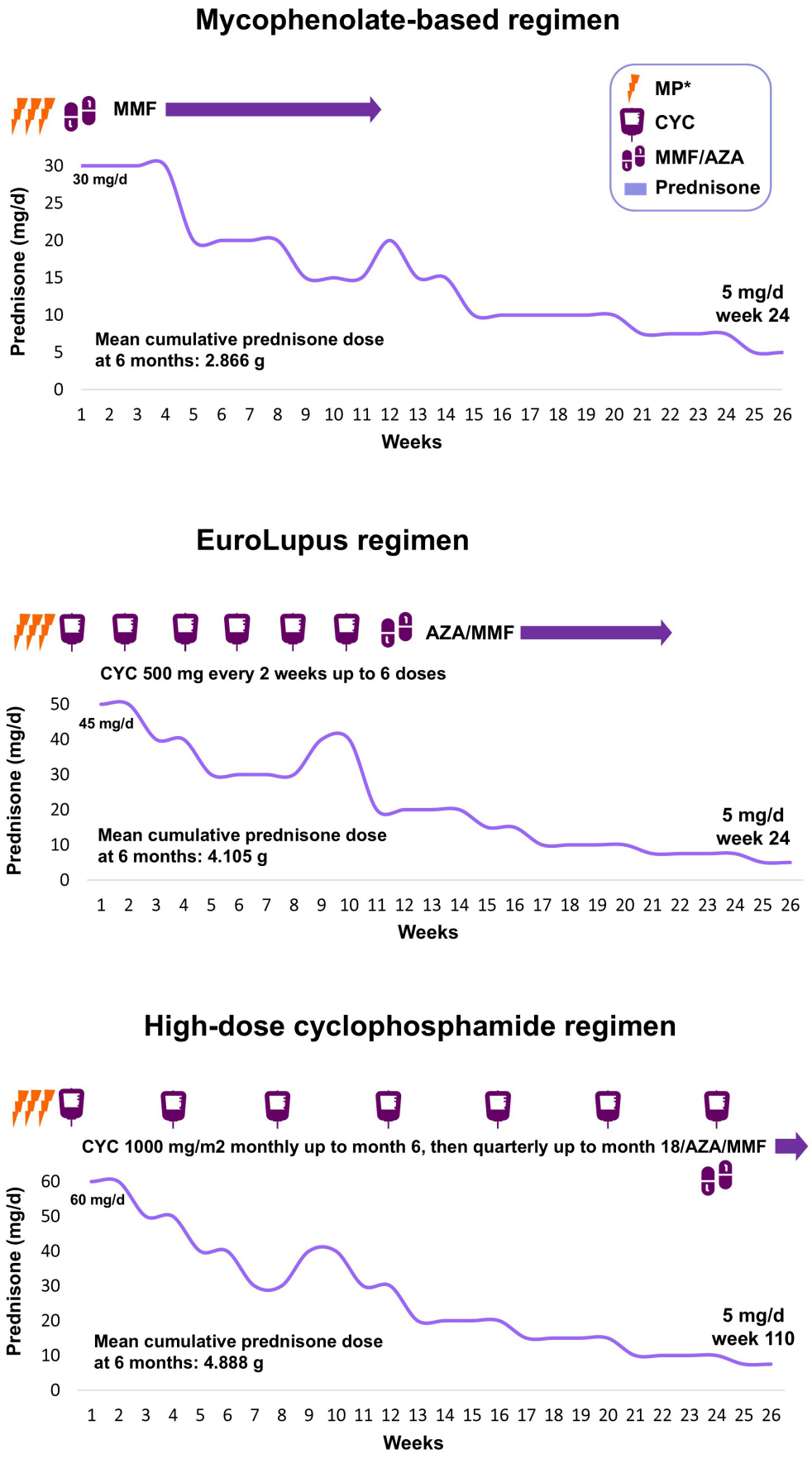

Figure 2 The different SOC therapeutic schemes. *MP x3 as per protocol in the Eurolupus scheme; according to clinical situation/clinician choice in MMF-based and high-dose CYC regimens. AZA, azathioprine; CYC, cyclophosphamide; MMF, mycophenolate; MP, methyl-prednisolone pulses; SOC, standard of care.

Outcome measures

We analysed four main outcomes:

1. The achievement of CRR, as defined in the 2024 Kidney Disease Improving Global Outcomes (KDIGO) guidelines[3]: reduction in the Pr/Cr<0.5 g/g and stabilisation or improvement in kidney function, ±10%–15% of baseline, at 12 months after the initiation of induction therapy, and time to CRR. Relapses after achieving CRR were also analysed.
2. The progression to CKD G3a or higher (ie, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2) according to the definition by KDIGO guidelines,[3] including haemodialysis and/or kidney transplant, which were labelled under ESKD.
3. The toxicity outcomes included the proportion of patients who developed GC-related side effects (defined as metabolic disorders, such as new-onset diabetes mellitus, hypercholesterolaemia, obesity and/or Cushingoid features, avascular osteonecrosis, osteoporotic fractures and/or cataracts) and the occurrence of major infections (those requiring hospitalisation and/or resulted in death).
4. The damage outcome consisted of new damage caused by LN, including the three renal items in the SLICC Damage Index,[17] or by GCs, including new osteonecrosis, osteoporotic fractures, diabetes or cataracts, as previously defined.[7]

Statistical analysis

Descriptive data were generated, using percentages, means and SDs or median with IQR, as indicated, for the whole cohort and for the two treatment groups (LCN and SOC). Data were compared by χ^2 test, Student's t-test and Mann-Whitney U test, as appropriate.

The proportions of patients achieving CRR at 6 and 12 months in each treatment group were compared by χ^2 test. Kaplan-Meier failure curves with log-rank test comparisons were calculated to describe the efficacy of both regimens (LCN and SOC) in achieving CRR over time, with non-responsive patients being censored at the end of the effective follow-up period or at a maximum of 10 years.

For the multivariate adjustment, a propensity score (PS) analysis was performed.[18] The individual PS, that is, the probability of being treated with the LCN protocol, was calculated for each patient by using a logistic regression model, in which age at the time of diagnosis of LN, gender, subcohort (BDX, Cruces-EAS, Cruces-historic), race (white vs non-white), LN class, first episode of LN vs relapse, baseline serum Cr and Pr/Cr levels, dose of HCQ and use of antiproteinuric drugs were the independent predictors. The discriminatory capacity of this model was assessed by the area under the receiver operating characteristic (ROC) curve with a resulting value of 0.75.

The PS was then used as an adjustment covariate in multivariate analyses: binary logistic regression models with CRR at 12 months as the dependent variable and Cox regression models comparing the time to CRR, CKD and damage in both groups.

χ^2 test was used to compare the frequency of GC toxicity or major infections in the two groups. Kaplan-Meier failure curves were calculated for the toxicity outcomes and compared with the log-rank test. Then, a Cox regression analysis for GC toxicity was performed, including the following adjusting variables: age, gender, smoking, antiphospholipid antibodies, treatment with vitamin D and PS. The Cox model for major infections was adjusted for PS.

The statistical analysis was performed using STATA/MP V.18 for Mac (StataCorp).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

Demographic and clinical variables

A total of 147 patients were included in this study: 47 in the LCN and 100 in the SOC group. The mean follow-up time was 341 vs 347 weeks, respectively, (p=0.84). Table 1 summarises the baseline characteristics of both groups.

Treatments

Important differences were found regarding treatment schemes between both groups (table 1). Lower initial doses of prednisone were used in the LCN group (22 vs 43 mg/day in the SOC group, p<0.001). Also, patients in the LCN group had a quicker tapering of prednisone to 5 mg/day compared with the SOC group (median 12 vs 24 weeks, respectively, p<0.001), with resulting lower cumulative doses of prednisone during the first 6 months (table 1).

All patients in the LCN group received MP, compared with 54% in the SOC group (p<0.001). The respective median number of pulses per patient during the first 6 months of therapy was 10 vs 3 (p<0.001).

HCQ was used in 100% LCN patients vs 56% SOC patients (p<0.001). All patients in the LCN groups were given CYC vs 62% in the SOC group (p<0.001). There were no significant differences between both groups regarding the use of MMF or azathioprine. The use of antiproteinuric drugs and vitamin D was higher in the LCN group (table 1).

Complete renal response

Table 2 summarises the main outcomes. More patients in the LCN achieved CRR at 12 months (85% vs 44%, respectively, p<0.001). The PS-adjusted logistic regression model confirmed the independent effect of the LCN regimen in achieving 12-month CRR (PS-adjusted OR 7.2, 95% CI 2.8 to 18.6, table 3).

Eventually, 96% patients in the LCN group achieved CRR vs 74% patients in the SOC (p=0.002), with a

Table 1 Baseline clinical characteristics and therapy by treatment group

	Total (N=147)	LCN (N=47)	SOC (N=100)	P value
Site				<0.001
Bordeaux	43 (29.3%)	0 (0%)	43 (43%)	
Cruces	104 (70.7%)	47 (100%)	57 (57%)	
Age at LN (years); mean (SD)	35 (13.4)	35.8 (13.7)	34.7 (13.3)	0.63
Female	118 (80.3%)	36 (76.6%)	82 (82%)	0.44
Clinical features				
Rash	98 (66.7%)	29 (61.7%)	69 (69%)	0.38
Arthritis	116 (78.9%)	34 (72.3%)	82 (82%)	0.18
Serositis	49 (33.3%)	18 (38.3%)	31 (31%)	0.38
Haematologic	69 (46.9%)	17 (36.2%)	52 (52%)	0.07
APS	13 (8.8%)	4 (8.5%)	9 (9%)	0.92
White	117 (79.6%)	32 (68.1%)	85 (85%)	0.02
Smoking	52 (35.4%)	20 (42.6%)	32 (32%)	0.21
CV risk factors				
Hypertension	35 (23.8%)	7 (14.9%)	28 (28%)	0.08
Diabetes	2 (1.4%)	0 (0%)	2 (2%)	0.32
Dyslipidaemia	33 (25.2%)	6 (12.8%)	27 (32.1%)	0.01
Obesity	20 (13.7%)	11 (23.4%)	9 (9.1%)	0.01
Antibodies				
Anti-DNA	132 (89.8%)	41 (87.2%)	91 (91%)	0.48
Anti-Ro	61 (41.5%)	26 (55.3%)	35 (35%)	0.02
Anti-La	24 (16.3%)	11 (23.4%)	13 (13%)	0.11
Anti-RNP	36 (24.5%)	12 (25.5%)	24 (24%)	0.84
Anti-Sm	33 (22.4%)	10 (21.3%)	23 (23%)	0.81
aPL	32 (21.8%)	9 (19.1%)	23 (23%)	0.59
Complement levels (mg/dL); mean (SD)				0.40
C3	59.8 (29.2)	56.9 (23.4)	61.2 (31.6)	
C4	10.2 (8.2)	8.1 (5.3)	11.2 (9.1)	
LN class				0.40
Class III	40 (27.2%)	11 (23.4%)	29 (29%)	
Class IV	89 (60.5%)	32 (68.1%)	57 (57%)	
Class V	18 (12.2%)	4 (8.5%)	14 (14%)	
First episode of LN	99 (67.3%)	34 (72.3%)	65 (65%)	0.37
Pr/Cr (g/g); mean (SD)	3.2 (2.9)	3.15 (3.51)	3.3 (2.67)	0.72
Serum Cr (mg/dL); mean (SD)	1.06 (0.69)	0.9 (0.34)	1.1 (0.8)	0.16
Serum albumin (mg/dL); mean (SD)	2.97 (0.69)	3.1 (0.72)	2.8 (0.67)	0.02
Initial dose of prednisone (mg/day); mean (SD)	36.3 (19.6)	22 (6.9)	43 (20.2)	<0.001
Weeks until prednisone ≤5 mg/day; median (IQR)	24 (12–40)	12 (10–14)	24 (24–100)	<0.001
Prednisone cumulative dose in 6 months (g); mean (SD)	3.28 (2.28)	1.42 (0.22)	4.18 (2.29)	<0.001
MP	101 (68.7%)	47 (100%)	54 (54%)	<0.001
Number of MP in 6 months; median (IQR)*	6 (3–10)	10 (9–12)	3 (3–3)	<0.001
Cumulative MP dose in 6 months (g); median (IQR)*	1.875 (1.125–2.25)	1.875 (1.5–2.25)	2.25 (0.75–2.25)	0.4
HCQ	103 (70%)	47 (100%)	56 (56%)	<0.001
HCQ dose (mg/day); mean (SD)*	262 (107.6)	217 (56.4)	300 (125)	0.06

Continued

Table 1 Continued

	Total (N=147)	LCN (N=47)	SOC (N=100)	P value
Weeks on HCQ in 6 months; mean (SD)*	24.8 (3.7)	26 (0)	24 (4.9)	0.004
CYC	109 (74%)	47 (100%)	62 (62%)	<0.001
Cumulative CYC dose in 6 months (g); mean (SD)*	4.2 (2)	3.5 (1.3)	4.8 (2.3)	<0.001
MMF	88 (60%)	28 (60%)	60 (60%)	0.96
Azathioprine	54 (37%)	19 (40%)	35 (35%)	0.52
Antiproteinuric drugs	86 (58.5%)	34 (72.3%)	52 (52%)	0.02
Vitamin D	92 (62.6%)	40 (85.1%)	52 (52%)	<0.001

*In patients taking the drug.
aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; Cr, serum creatinine; CV, cardiovascular; CYC, cyclophosphamide; HCQ, hydroxychloroquine; LCN, Lupus-Cruces Nephritis group; LN, lupus nephritis; MMF, mycophenolate; MP, methyl-prednisolone pulses; Pr/Cr, urinary protein/creatinine ratio; SOC, standard of care.

median time to CRR of 21 vs 48 weeks, respectively (p<0.001). The Kaplan-Meier curves for CRR can be seen in figure 3. In the PS-adjusted Cox model, LCN patients were 3.5-fold more likely to eventually achieve CRR (table 3).

Chronic kidney disease

Progression to CKD G3a or higher during the follow-up time happened in 10.6% vs 27% in LCN and SOC patients, respectively (p=0.02, table 2), with an HR 0.3 (95% CI 0.11 to 0.82) in the PS-adjusted Cox analysis (table 3). The Kaplan-Meier curves for progression to CKD can be seen in figure 3. Eight patients (5.4% of the whole cohort) developed ESKD, all of them in the SOC group (p=0.05)

Relapses

Among the 119 patients achieving CRR, 28.8% in the LCN vs 25.7% patients in the SOC group relapsed (p=0.7, table 2). The median time to relapse after CRR was 250 vs 211 weeks, respectively (p=0.2). In the survival analysis, neither the log-rank test (p=0.9) nor the Cox regression (PS-adjusted HR 1, 95% CI 0.45 to 2.2, p=0.9) found

Table 2 Outcome variables by group

	Total (N=147)	LCN (N=47)	SOC (N=100)	P value
CRR at 6 months	53 (36.1%)	28 (59.6%)	25 (25%)	<0.001
CRR at 12 months	84 (57.1%)	40 (85%)	44 (44%)	<0.001
CRR at 12 months with no need for additional treatments	76 (51.7%)	34 (72%)	42 (42%)	<0.001
CRR at any time	119 (81%)	45 (96%)	74 (74%)	0.002
Weeks until CR; median (IQR)*	34 (16–60)	21 (12–39)	48 (24–76)	<0.001
Any relapse during follow-up*	32 (26.8%)	13 (28.8%)	19 (25.7%)	0.7
Progression to CKD	32 (21.8%)	5 (10.6%)	27 (27%)	0.02
Progression to ESKD	8 (5.4%)	0 (0%)	8 (8%)	0.05
Renal/GC-induced damage	49 (33%)	6 (12.7%)	37 (37%)	0.003
GC-related toxicity	47 (32%)	2 (4%)	45 (45%)	<0.001
Metabolic toxicity	43 (29%)	1 (2.1%)	42 (42%)	<0.001
Bone toxicity	13 (8.8%)	1 (2.1%)	12 (12%)	0.049
OP fracture	3 (2%)	1 (2.1%)	2 (2%)	0.95
Osteonecrosis	10 (6.8%)	0 (0%)	10 (10%)	0.025
Cataracts	3 (2%)	0 (0%)	3 (3%)	0.23
Major infections	17 (11.6%)	2 (4.3%)	15 (15%)	0.05

*In patients achieving CRR.
CKD, chronic kidney disease G3a or higher; CRR, complete renal response; ESKD, end-stage kidney disease; GC, glucocorticoid; LCN, Lupus-Cruces Nephritis group; OP, osteoporotic; SOC, standard of care.

Table 3 PS-adjusted multivariate analysis (LCN vs SOC)

Outcome	OR/HR (95% CI)	P value
CRR at 12 months	OR 7.2 (95% CI 2.8 to 18.6)*	<0.001
CRR at 12 months without additional treatment	OR 3.5 (95% CI 1.5 to 7.9)*	0.002
CRR during follow-up	HR 3.5 (95% CI 2.2 to 5.5)†	<0.001
CKD during follow-up	HR 0.3 (95% CI 0.11 to 0.82)†	0.019
Relapse after CRR	HR 1, (95% CI 0.45 to 2.2)†	0.9
Renal/GC-induced damage	HR 0.26 (95% CI 0.11 to 0.64)†	0.003
GC-related toxicity	HR 0.09 (95% CI 0.02 to 0.39)‡	0.001
Major infections	HR 0.2, (95% CI 0.046 to 0.95)†	0.04

*Logistic regression.
†Cox regression.
‡Cox regression adjusted by age, gender, smoking status, aPL-positivity, treatment with vitamin D and PS.
CKD, chronic kidney disease G3a or higher; CRR, complete renal response; LCN, Lupus-Cruces Nephritis group; PS, propensity score; SOC, standard of care.

significant differences in relapsing LN between both groups (table 3).

Toxicity

Toxicity in both groups is summarised on tables 2 and 3. Fewer patients in the LCN group suffered GC-related toxicity during the follow-up (4% vs 45%, p<0.001), with an HR 0.09 (95% CI 0.02 to 0.39) in the adjusted Cox analysis. It is particularly remarkable that no patients in the LCN group ever developed osteonecrosis, compared with 10% SOC patients (p=0.025). Major infections were seen in 4.3% LCN vs 15% SOC patients, p=0.05, with a PS-adjusted HR 0.2 (95% CI 0.046 to 0.95). The Kaplan-Meier curves for GC toxicity and major infections are shown in figure 3.

Damage

Likewise, patients in the LCN group were less likely to accrue renal/GC-related damage during the follow-up: 12.7% vs 37%, p=0.003 (table 2). The PS-adjusted HR was 0.26 (95% CI 0.11 to 0.64, table 3). The Kaplan-Meier curves for renal/GC-induced damage are shown in figure 3.

Subgroup analyses

Analysis excluding the Cruces-historic subcohort

In the efficacy analysis by subcohorts within the SOC group, the respective rates of CRR at 12 months for the BDX (n=43), Cruces-EAS (n=15) and Cruces-historic (n=42) groups were 51%, 53% and 33%, respectively (p=0.18). The baseline and some therapeutic characteristics of the Cruces-historic cohort (see online supplemental table S1) could have influenced such results. Therefore, we repeated the efficacy analysis in 105 patients after excluding the Cruces-historic cohort from the SOC group.

The results regarding CRR were very much alike those seen in the whole group (online supplemental table S2): CRR at 12 months, 85% vs 51% in LCN and SOC, respectively, (p<0.001); PS-adjusted OR for CRR at 12 months, 5.3 (95% CI 1.9 to 14.8); PS-adjusted HR for CRR during follow-up, 2.7 (95% CI 1.6 to 4.4); PS-adjusted HR for progression to CKD, 0.36 (95% CI 0.12 to 1.07).

CYC-treated groups

Three different CYC-based schemes were used in 109 patients: the LCN protocol (n=47), the Eurolupus scheme[19] and the high-dose CYC scheme (n=34). The rate of CRR at 12 months was higher in the LCN group (85% vs 57% vs 29%, respectively, p<0.001) and the progression to CKD lower (10.6% vs 21.4% vs 32.3, respectively, p=0.05).

Analysis by race

Considering the influence of race in the response to immunosuppressive drugs,[20] we performed the efficacy analysis separately for white (n=117) and non-white (n=30) patients (online supplemental table S3). Within white patients, the CRR rates at 12 months for LCN and SOC patients were 90.6% vs 46% (p<0.001), with a PS-adjusted OR 10.1 (95% CI 2.8 to 36.6). The Cox regression showed a PS-adjusted HR for CRR 3.7 (95% CI 2.2 to 6.1). Progression to CKD over time was less likely: PS-adjusted HR 0.34, (95% CI 0.09 to 1.2). In non-white patients, differences between treatment groups also favoured the LCN group (12-month CRR rates, 73% vs 33%, p=0.03), although the low sample size widened CIs: CRR at 12 months, PS-adjusted OR 5.2 (95% CI 0.98 to 27.8); CRR during follow-up, PS-adjusted HR 3.3 (95% CI 1.3 to 8.5); progression to CKD, PS-adjusted HR 0.28, (95% CI 0.05 to 1.4).

Class V LN

The outcome of patients with class V LN (n=18) was independently analysed. Patients in the LCN group had a 100% CRR rate at 12 months, vs 28.5% among patients in the SOC group (p=0.023). The PS-adjusted HR for CRR was 19 (95% CI 2.2 to 160.9). No patients with class V LN in the LCN group progressed to CKD, vs 35% in the SOC group (p=0.16).

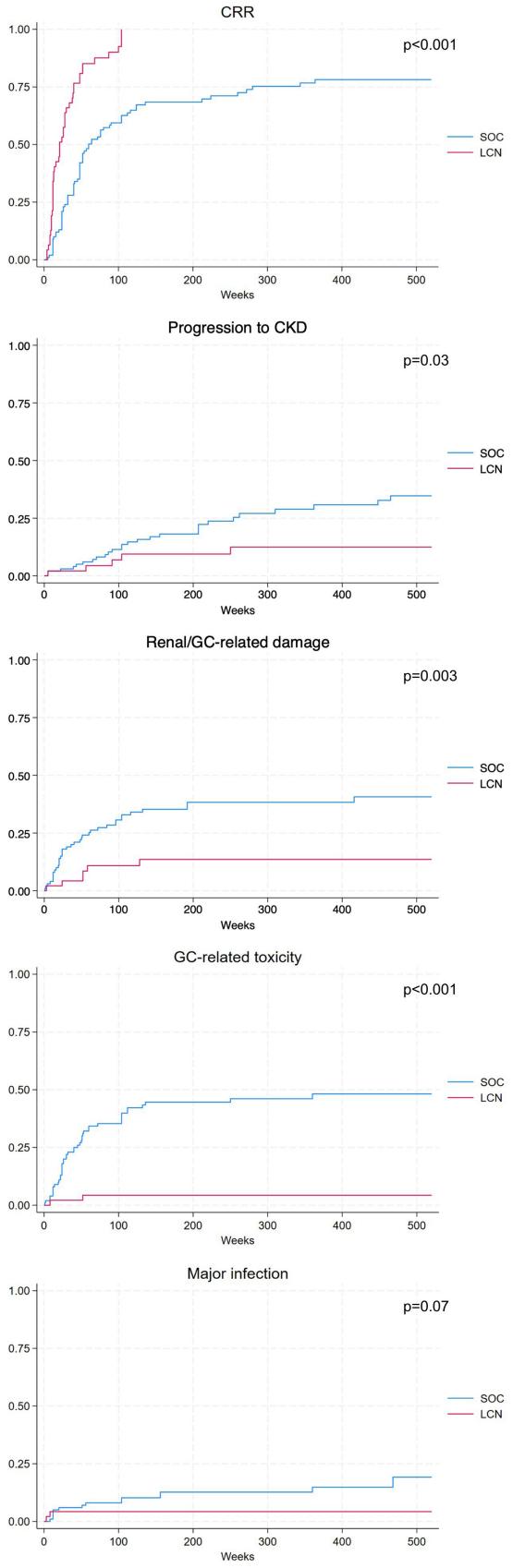

Figure 3 Kaplan-Meier curves for efficacy and toxicity outcomes (LCN vs SOC, n=147). CKD, chronic kidney disease G3a or higher; CRR, complete renal response; GC, glucocorticoid; LCN, Lupus-Cruces Nephritis; SOC, standard of care.

Need for additional therapy

Ten patients (21%) needed additional therapy within the first year in the LCN group vs 17 (17%) in the SOC group (p=0.53). Considering patients needing additional drugs as non-responders, 72% LCN patients achieved CRR at 12 months vs 42% SOC patients (p<0.001, table 2), with a PS-adjusted OR 3.5, 95% CI 1.5 to 7.9 (table 3).

Within the LCN group, the reasons for adding therapy were as follows: progression of LN (n=6), multisystemic disease at presentation (n=3) and non-controlled extra-renal disease (n=1). Additional therapy was administered in 9/10 patients before the first 6 months. Five patients received rituximab alone, three rituximab followed by belimumab plus tacrolimus and two belimumab alone. Five patients achieved CRR within 12 months and 3 more patients during the second year of follow-up, thus 80% eventually achieving CRR. The two patients who did not respond even after adding new therapies were the only ones in this LCN subgroup who progressed to CKD.

DISCUSSION

Patients with LN not achieving CRR have a higher risk of progressing to CKD, including ESKD.[4 21] CRR rates with conventional immunosuppressives (CYC or MMF) have been reported at variable rates ranging from 30% to 70% patients.[12 22–24] Moreover, the rate of progression to ESKD among patients with LN in developed countries has been shown to increase after the early 2000s, following decades of improvement.[25] The logical consequence of such disappointing results was the urgent call for more efficient therapeutic regimens.

Within the last 5 years, two phase 3 randomised clinical trials (RCTs) have led to the approval of belimumab[26] and voclosporin[27] as add-on therapies to SOC with CYC (belimumab) or MMF (both of them) for the initial treatment of patients with LN. A more recent RCT has shown the superiority of adding the anti-CD20 monoclonal antibody obinutuzumab to SOC with MMF in achieving CRR at 76 weeks.[28] The availability of a wider number of treatment options for LN is really good news. However, CRR was achieved by 30%, 41% and 46.4% patients in the experimental arms,[26–28] numbers still insufficient and not really superior to those reported in real-life cohorts.[2 19 23 29 30] In addition, the cost of these new agents can greatly limit their accessibility for a large number of patients at a worldwide scale.

The current study analysed 147 biopsy-proven LN (classes III, IV and/or V) from two referral centres followed for a maximum of 10 years and confirmed our previous results,[9–11] in that the addition of repeated MP with each CYC dose (the LCN protocol) resulted in a faster (59.6% CRR at 6 months, 85% CRR at 12 months) and better response, with CRR being eventually achieved by 96% patients. Moreover, the prolonged follow-up of our cohort has allowed us to report a low progression rate to CKD (10.6% after a mean follow-up of 341 weeks), with no patients treated with the LCN protocol evolving

to ESKD to date. All these figures compare favourably with the SOC group. The better short-term and long-term effects of the LCN were seen across white and non-white patients and in both proliferative and membranous types of LN. An additional and essential benefit of the LCN protocol was the great reduction of oral GC load, which resulted in a marked decrease of GC-induced toxicity and serious infections. As a result, renal-or-GC-induced irreversible damage accrual was much lower with the LCN protocol.

The prednisone tapering scheme in the LCN protocol was first published in 2014, with the Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA) trial[27] as well as the most recent 2024 KDIGO guidelines for the management of LN[3] using very similar schemes, prednisone doses being reduced to ≤5 mg/day in 12 weeks. We believe that all the above make the LCN protocol for LN an effective and safe approach, in addition to widely available and affordable.

The cornerstone of the LCN protocol is the repeated use of MP. The selective activation of the non-genomic GC way by doses over 100 mg/day results in additional effects not seen with lower, genomic-only doses of prednisone.[31] MP activates the non-genomic pathway via the cytosolic GC receptor, inhibiting cytosolic PLA2 (cPLA2), or via the interaction with membrane GC receptor, inhibiting the p38 MAP kinase pathway or promoting cell apoptosis.[32] MP also promotes the differentiation of T-lymphocytes to long-lasting Tregs[33] and primes the cells for subsequent genomic effects.[34] Non-genomic activation leads not only to rapid and potent anti-inflammatory effects without genomic-mediated toxicity, but also to more long-lasting actions that result in higher rates of prolonged remission, as recently shown by our group.[35] Regarding LN, the addition of MP to moderate doses of oral prednisone has resulted in higher CRR rates, without the increase in serious infections and mortality seen with the combination of MP with high doses of prednisone.[22] However, MP is not always included in the induction regimen, nor are repeated MP recommended in the guidelines.[3 5 6] This study could help improve its routine use.

We acknowledge some limitations to our work. First, this is an observational, non-randomised study in which all patients receiving the LCN protocol were treated in the same centre. To overcome the potential confounding-by-indication bias, we conducted a PS analysis, in which a large number of clinical and demographic variables were included in the PS calculation. In addition, we performed a secondary analysis after excluding historic patients (who tended to achieve worse outcomes) and performed several subgroup analyses, all reinforcing the results in the whole cohort. Second, under certain indications, basically severe multisystemic disease or unfavourable renal progression, the LCN protocol also included the use of additional therapies (rituximab, belimumab and/or CNI). Such additional therapy was used early (90% within the first 6 months), with all the efficacy outcomes after considering such patients as non-responders being still favourable to the LCN group. For the 37 LCN patients not needing additional drugs, the rate of response was 95% at 12 months. The early use of additional therapy in refractory patients resulted in 70% of them achieving CRR. All these data suggest that there is time to add on other therapies to the LCN scheme in cases with unfavourable evolution, although a majority of patients would do well with the original CYC-MP-based scheme. Third, although there was no active search for side effects, including osteonecrosis or cataracts, that is, only symptomatic cases were counted, the lack of cases of osteonecrosis in LCN patients is consistent with data of the Lupus-Cruces cohort in previous studies.[7] Fourth, although this CYC-MP-based regimen demands intravenous drug administration in a day-hospital setting, this fact may also help maximise adherence to therapy and tighten clinical care during the most critical period of LN, which is an essential factor for the early detection (and additional therapy) of non-responders. Fifth, the relatively small sample size could have underpowered this study. However, the differences found between the LCN and SOC groups were large enough to attain statistical significance in most comparisons. Moreover, the 12-month CRR rates in the LCN group were very much alike those published in our previous, smaller, studies.[9 11] In addition, CRR was eventually achieved by more than 70% of patients in the SOC, thus the good results in the LCN were not obtained against bad results in the control group. Finally, although almost 80% patients were white, the subgroup analysis by race did not reveal any differences in the efficacy of the LCN protocol compared with SOC.

In conclusion, this study supports the efficacy and safety of the LCN protocol, a scheme consisting of the addition of repeated MP to biweekly CYC therapy, with a reduced starting dose and rapid fixed tapering of oral prednisone to 5 mg/day in 12 weeks. This scheme maximised the chance for an early CRR and reduced the progression to CKD and ESKD, GC-induced toxicity, infections and, eventually, damage accrual. We believe that this widely available and affordable drug combination could benefit patients with LN in a worldwide setting, including countries and individuals with reduced income and a limited access to more costly regimens.

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