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Prolonged remission in SLE is possible by using reduced doses of prednisone: An observational study from the Lupus-Cruces and Lupus-Bordeaux inception cohorts

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ABSTRACT

Objective: The aim of this study is to compare the frequency of remission, according to DORIS definitions, of inception patients from two European SLE cohorts, with a special focus on the differences between the therapeutic schemes of both Units.
Methods: Inception patients enrolled after 2000 from the longitudinal Cruces Lupus Cohort (CC) and Bordeaux Lupus Cohort (BC) were included. The main endpoint was the achievement of clinical remission on treatment (ClinROnT). ClinROnT was assessed yearly from the 1st until the 5th year following the diagnosis of SLE.
Results: 173 patients, 92 CC and 81 BC, were studied. The clinical presentation of both cohorts was similar, with no significant differences in the mean SLEDAI score at diagnosis (6.6 vs. 8.1, $p = 0.06$). Patients from CC were treated more frequently with hydroxychloroquine (mean 57 vs. 43 months), methotrexate (24% vs. 11%) and pulse methyl-prednisolone (42% vs. 26%), and received lower doses of oral prednisone (average dose during the follow up 2.3 vs. 7.2 mg/d, $p < 0.001$). Patients in CC were more likely to achieve ClinROnT at year one, 84% vs. 43% ($p < 0.001$). Prolonged ClinROnT during the 5 years of follow up was more frequent in CC: 70% vs. 28%, $p < 0.001$. Patients in CC were also more likely to achieve ClinROnT after controlling for baseline SLEDAI (adjusted HR 1.69, 95%CI 1.21–2.35) and for the presenting clinical manifestations (adjusted HR 1.72, 95% CI 1.2–2.4).
Conclusion: Prolonged ClinROnT was achievable by using a therapeutic regime consisting of lower doses of oral prednisone and maximizing the use of hydroxychloroquine, pulse methyl-prednisolone and methotrexate.

1. Introduction

SLE is an extraordinarily heterogeneous disease with a broad spectrum of manifestations. It frequently runs a relapsing-remitting pattern, with flares of activity that can range from mild to severe [1,2]. In the last decades, a remarkable improvement in the prognosis of SLE has been observed, mostly due to a better understanding of the disease and to the advent of new therapies [3]; however, shared treatment strategies and validated outcome measures are still lacking [4]. It is now well known that disease activity is linked to increased organ damage and mortality per se, but also due to the consequent use of higher doses of glucocorticoids [5]. Thus, both control of activity and reduction of glucocorticoid burden are key targets [6].

It is not surprising that the concept of remission has emerged as an important goal in recent years. This term has been extensively discussed and studies on this topic published from 1970 to 2014 have used a large

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number of different definitions [7]. In 2015, an initiative to achieve the unification of definitions was undertaken by an international task force (DORIS - Definition Of Remission in SLE) [8]. Four different levels of remission were agreed, according to the presence of clinical and serological activity and treatments received: complete remission (ComR), clinical remission (ClinR), complete remission on treatment (ComROnT) and clinical remission on treatment (ClinROnT). The Lupus Low Disease Activity State (LDA) has recently been developed by the Asia-Pacific Lupus Collaboration [9]. This concept is less restrictive and allows mild disease activity without involvement of major organ systems. It has been shown that remission over two years or more is associated with a decrease in organ damage [10]. However, whether sustained remission is an achievable goal is a matter of debate [11].

The aim of this study was to compare the frequency of remission, according to DORIS definitions, of inception patients from two well characterised European SLE cohorts, the Lupus-Cruces and the Lupus-Bordeaux cohorts, during a 5-year follow-up period, with a special analysis of the differences between the therapeutic schemes of both Units.

2. Patients and methods

2.1. Study design and patients

We conducted a comparison study between two longitudinal SLE cohorts, the Spanish Cruces University Hospital Cohort (CC) and the French Bordeaux University Hospital Cohort (BC). Both are observational lupus cohorts based at University hospitals aimed to identify prognostic factors in SLE, with particular focus on therapy.

Eligible patients fulfilled the revised ACR or SLICC criteria for the classification of SLE [12,13]. The point when classification criteria were met was considered time 0 of follow-up. Only patients diagnosed after year 2000 and treated since time 0 at the respective centres (inception patients) were included in the study, in order to avoid bias related with previous therapies administered by referring physicians outside our two Units.

The study protocol was approved by the institutional review boards and ethic committees of Hospital Universitario Cruces and Bordeaux University Hospital. All participants signed an informed consent form before being included in the databases.

2.2. Treatment protocols

All patients were aimed to receive hydroxychloroquine (HCQ). Glucocorticoids and immunosuppressive drugs were given according to disease activity, specific lupus manifestations and attending physicians' judgement; however, some general protocol differences did exist between both Units.

Patients from CC were, by protocol, never treated with doses of prednisone > 30 mg/d; instead, methyl-prednisolone pulses of 125, 250 or, in severe cases, 500 mg/×3 consecutive days were preferentially prescribed to treat acute disease flares, even those with non-major organ involvement. Likewise, prednisone maintenance doses were never > 5 mg/d, early immunosuppressive drugs being used in case this objective could not be accomplished [14,15]. Patients with lupus nephritis were managed according to the Lupus-Cruces nephritis protocol, as previously detailed [16].

Patients from BC were treated according currently accepted guidelines [17–19]. Oral prednisone was generally initiated at a dose of 0.7–1.0 mg/kg/d, and reduced by 2.5–5.0 mg every 2 to 4 weeks until the long-term maintenance dose. Maintenance therapy usually included low-dose glucocorticoid [5–7.5 mg/d) ± azathioprine or mycophenolate mofetil for several years. Methyl-prednisolone pulses were used in the setting of severe visceral involvement (renal, neurological, severe thrombocytopenia or hemolytic anemia), at a usual dose of 1000 mg/d ×3 consecutive days.

Table 1
Demographic, clinical and therapeutic variables.

	Bordeaux (n = 81)	Cruces (n = 92)	p value
Baseline variables			
Gender (female/male)	73/8	75/17	0.165
Age at diagnosis (years) mean (SD)	38 (14.4)	40 (15.3)	0.345
Caucasian n (%)	72 (89%)	86 (94%)	0.075
Smoking ever n (%)	28 (35%)	52 (57%)	0.006
Anti-Ro n (%)	23 (28%)	29 (32%)	0.778
Anti-La n (%)	8 (10%)	14 (15%)	0.410
Anti-RNP n (%)	15 (19%)	19 (21%)	0.872
Anti-Sm n (%)	10 (12%)	16 (17%)	0.476
Antiphospholipid ×2 n (%)	17 (21%)	28 (30%)	0.215
Anti-DNA n (%)	50 (62%)	54 (59%)	0.802
Low complement (C3, C4) n (%)	48 (59%)	56 (61%)	0.952
SLE manifestations at diagnosis n (%)			
Cutaneous	57 (70%)	68 (74%)	0.727
Articular	73 (90%)	62 (68%)	0.001
Serosal	10 (12%)	12 (13%)	1.000
Renal	14 (17%)	15 (16%)	0.86
Hematological	8 (10%)	3 (3%)	0.142
CNS involvement	6 (7%)	3 (3%)	0.378
Antiphospholipid Syndrome	6 (7%)	2 (2%)	0.203
SLEDAI at baseline mean (SD)	8.1 (4.9)	6.6 (5.4)	0.060
Treatment for SLE			
HCQ ever n (%)	74 (91%)	92 (100%)	0.013
HCQ at year 1 visit n (%)	65 (80%)	89 (97%)	0.001
HCQ at year 5 visit n (%)	59 (73%)	91 (99%)	< 0.001
Cumulative months on HCQ at year 1 visit mean (SD)	8.7 (0.5)	10.8 (0.3)	< 0.001
Cumulative months on HCQ during the follow-up mean (SD)	43.6 (2.5)	57.3 (0.8)	< 0.001
Prednisone ever n (%)	70 (86%)	78 (84%)	0.76
Prednisone at year 1 visit n (%)	64 (79%)	66 (72%)	0.353
Average dose of Prednisone during the follow-up (mg/d) mean (SD)[a]	7.2 (2.6)	2.3 (1.6)	< 0.001
Maximum dose of Prednisone (mg/day) mean (SD)[a]			
Within year 1	37 (20.4)	15 (9.8)	< 0.001
Within year 2	12 (12)	5 (4)	< 0.001
Within year 3	10 (7)	6 (6)	< 0.001
Within year 4	10 (7)	5 (4)	< 0.001
Within year 5	12 (12)	4 (2)	< 0.001
Prednisone ≤5 mg/d n (%)			
At year 1 visit	36 (44%)	89 (97%)	< 0.001
At year 2 visit	59 (73%)	89 (97%)	< 0.001
At year 3 visit	61 (75%)	90 (98%)	< 0.001
At year 4 visit	61 (75%)	91 (99%)	< 0.001
At year 5 visit	66 (81%)	91 (99%)	< 0.001
MP pulses ever n (%)	21 (26%)	39 (42%)	0.035
Number of MP pulses per patient mean (SD)[a]	3.3 (1.6)	7.4 (5.2)	0.001
Cumulative MP dose per patient (mg) mean (SD)[a]	1725 (1924)	1635 (1391)	0.835
IS ever n (%)	34 (42%)	47 (51%)	0.296
IS at year 1 visit n (%)	23 (28%)	32 (35%)	0.461
Cumulative months on IS during the follow-up mean (SD)[a]	39 (23.5)	41 (17.9)	0.684
MTX ever n (%)	9 (11%)	22 (24%)	0.028
MTX at year 1 visit n (%)	2 (2.5%)	110 (11%)	0.03

SLE: systemic lupus erythematosus; CNS: central nervous system; MP: methyl-prednisolone; HCQ: hydroxychloroquine; IS: immunosuppressive drugs; MTX: methotrexate.
SD: standard deviation.
[a] Calculated for patients taking the analysed drug.

2.3. Baseline variables

We compared baseline variables of both cohorts: gender, age, ethnicity, SLE manifestations, autoantibody profile (anti-DNA, anti-Ro, anti-La, anti-RNP, anti-Sm and antiphospholipid antibodies), low complement levels, and SLEDAI 2K [20] at enrolment.

We also compared both groups with regard to therapeutic variables

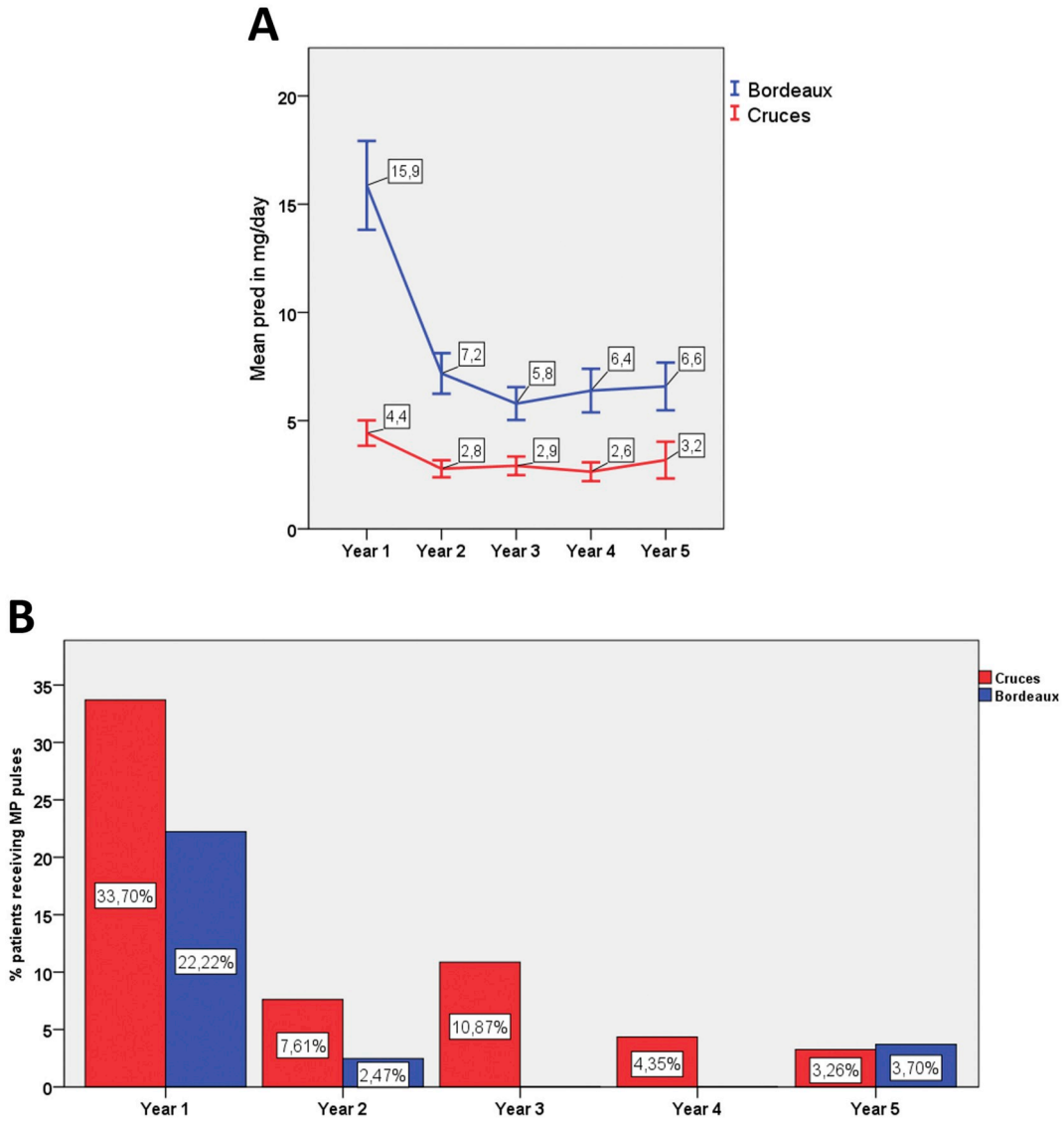

Fig. 1. Mean dose of prednisone in mg/d (A) and proportion of patients given methyl-prednisolone pulses (B) during the 5 years of follow up.
Footnote:
MP: methyl-prednisolone pulses; pred: prednisone.

assessed yearly, from year 1 to year 5: proportion of patients receiving prednisone, methyl-prednisolone, HCQ, azathioprine, methotrexate, cyclophosphamide and mycophenolate; maximum prednisone dose (received for at least 3 consecutive days); average daily prednisone dose; number of pulses of iv methyl-prednisolone; cumulative methyl-prednisolone dose; and number of months on HCQ.

2.4. Outcome measures

The main outcome variable was the achievement of ClinROnT, according to DORIS definitions [8]. To be in ClinROnT, the clinical SLEDAI (i.e. excluding the anti-DNA and complement items) had to be 0 and the physician global assessment (PGA) < 0.5; treatment with HCQ, immunosuppressive drugs and/or prednisone ≤ 5 mg/d were allowed. ClinROnT is very similar to the concept of low disease activity (LDA) used in similar studies, both of them predicting less damage accrual [21]. However, ClinROnT is more restrictive than LDA regarding the dose of prednisone allowed (5 mg/d vs. 7.5 mg/d) and the activity in non-major organ systems [8,9].

Other DORIS remission categories [8], ClinR, ComR and ComROnT were considered as secondary outcome variables for comparison between both cohorts. Of note, as ClinROnT is the less stringent type of remission, all patients fulfilling criteria for the other three types of remission were also classified as being in ClinROnT.

All types of remission were assessed yearly (year 1 to 5) after the diagnosis of SLE. Early remission achieved at year 1 was considered early remission. Prolonged remission was considered when patients fulfilled the respective remission criteria during the five consecutive yearly visits. SLEDAI scores calculated yearly were also compared.

2.5. Statistical analysis

Descriptive data were generated, using percentages, means and standard deviations (SD). Baseline and therapeutic data were compared by Chi-squared test, Fisher's exact test or unpaired Student's *t*-test, as appropriate.

Remission rates at year 1, 2, 3, 4 and 5 and prolonged remission rates were compared by Chi-squared. Kaplan Meier curves were built for time-dependent first ClinROnT and compared using log-rank test. Cox regression analysis was performed with ClinROnT as the dependent variable, cohort (CC or BC) as the main independent variable and baseline SLEDAI score or baseline clinical manifestations (nephritis,

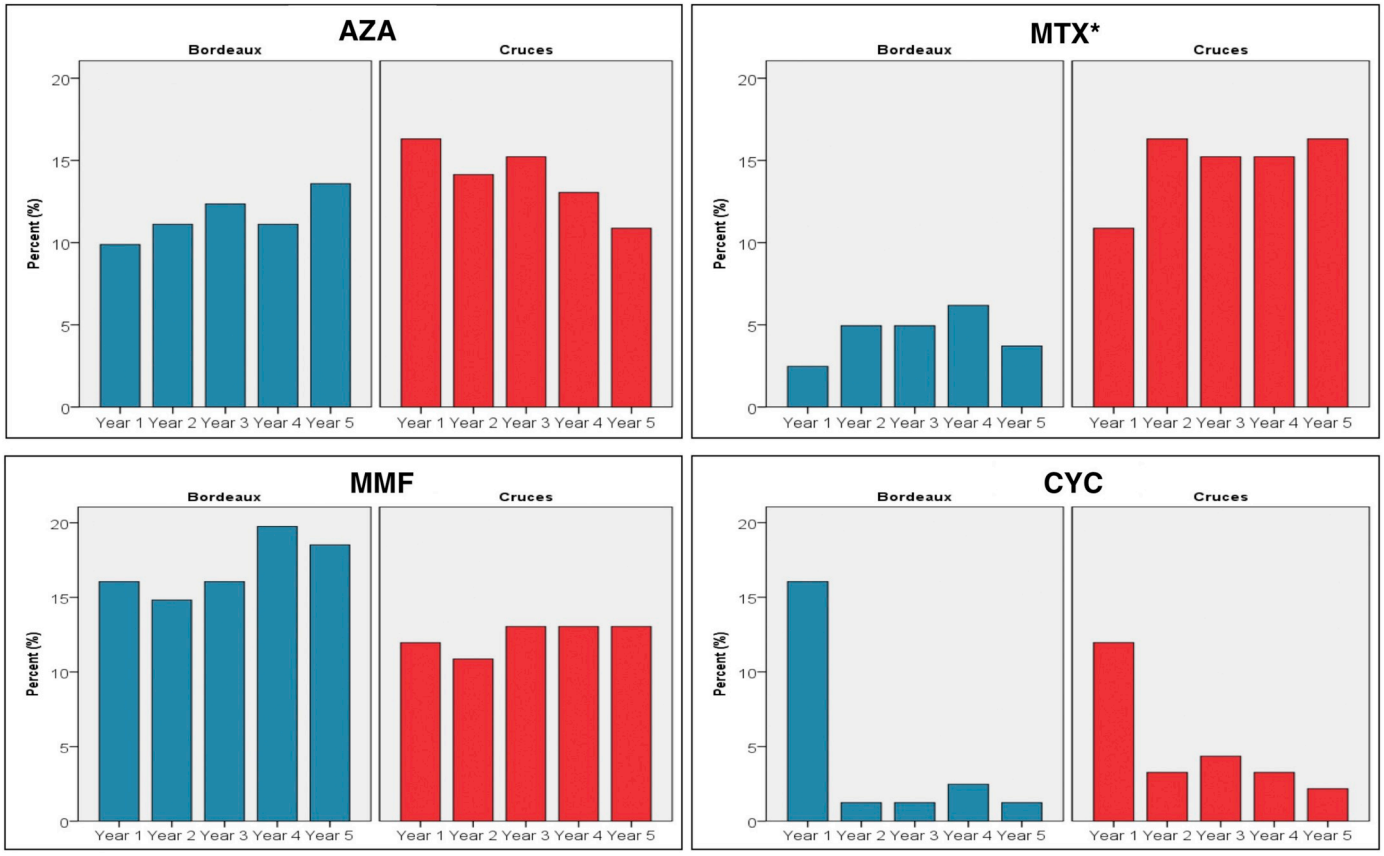

Fig. 2. Proportion of patients in treatment with immunosuppressive drugs during the follow-up.
Footnote:
AZA: azathioprine MTX: Methotrexate. MMF: Mycophenolate mofetil. CYC: Cyclophosphamide.
* $p < 0.05$ at each yearly comparison.

neurological, cutaneous, articular, serosal and hematological) as the adjusting variables.

A specific analysis of early ClinROnT was performed. This included comparisons of both cohorts stratifying patients by baseline SLEDAI scores 0–5, 6–12 and > 12 and by presenting clinical manifestations (nephritis, neurological, cutaneous, articular, serosal and hematological). Baseline SLEDAI scores or baseline clinical manifestations were used as adjustment variables in the logistic regression using early ClinROnT as the dependent variable and cohort (CC or BC) as the main independent variable.

The statistical analysis was done using STATA/MP 14.2 for Mac (StataCorp LP, TX, USA).

3. Results

3.1. Demographic and clinical variables

A total of 173 patients were studied: 92 from CC and 81 from BC. Baseline variables were similar between both groups except for a higher number of ever smokers in CC. There were no differences in the auto-antibody profile, while there was a higher frequency of articular manifestations among patients from the BC. There was a trend for a higher mean (SD) SLEDAI score at diagnosis in BC: 8.1 (4.9) vs. 6.6 (5.4) in CC, $p = 0.060$ (Table 1).

3.2. Treatments (Table 1)

The therapeutic approach in the two cohorts differed. The use of HCQ was higher in CC since the diagnosis: 97% patients in CC received HCQ during year 1 vs. 80% in BC ($p = 0.001$). While this proportion increased in CC at year 5 (99%), it actually decreased in BC (73%, $p < 0.001$), mainly due to concerns about retinal toxicity. In consequence, patients in CC had a significantly higher number of months on treatment with HCQ, both at the end of the 1st and the 5th year of follow up (difference 2 months and 13.6 months, respectively).

While the proportion of patients on oral prednisone was similar in both groups, marked differences were found regarding the dose. No patients in CC ever received prednisone > 30 mg/d, vs. 42% in BC ($p < 0.001$). The average daily dose per year was lower in the CC during the 5 years of the study (Fig. 1a). This was true for patients presenting with mild (1.9 mg/d vs. 5.6 mg/d, respectively, $p < 0.001$), moderate (2.4 mg/d vs. 6.8 mg/d, respectively, $p < 0.001$) or severe activity (3.8 mg/d vs. 10.3 mg/d, respectively, $p < 0.001$) at enrolment. Likewise, maximum prednisone doses were lower and the proportion of patients on prednisone ≤5 mg/d was significantly higher in CC during the follow up (Table 1).

Methyl-prednisolone pulses were used more frequently in CC (42% vs. 26%), with a significantly higher mean number of total pulses per patient, 7.4 vs. 3.3, respectively. However, the mean total dose of methyl-prednisolone per patient was similar in both cohorts, explained by a lower dose per pulse in CC. In both groups, pulses were mainly given within the 1st year after the diagnosis of SLE (Fig. 1b). Of note, the difference was more marked in patients presenting with a baseline SLEDAI 6–12 (55% vs. 16%, respectively, $p < 0.001$).

The proportion of patients ever receiving immunosuppressive drugs was similar in both groups. As for the specific type of drug, there were no differences in the use of cyclophosphamide, azathioprine and mycophenolate (Fig. 2). However, methotrexate was ever given to 24% of

Table 2
Activity and remission during the follow-up.

	Bordeaux (n = 81)	Cruces (n = 92)	p value
Disease activity			
SLEDAI at year 1 mean (SD)	2.0 (1.9)	2.3 (2.5)	0.306
SLEDAI at year 2 mean (SD)	1.8 (1.7)	2.0 (2.5)	0.529
SLEDAI at year 3 mean (SD)	2.0 (1.8)	1.9 (2.4)	0.694
SLEDAI at year 4 mean (SD)	1.8 (1.8)	1.7 (2.1)	0.692
SLEDAI at year 5 mean (SD)	1.8 (2.1)	1.6 (1.7)	0.443
Type of remission			
Clinical remission on treatment			
At year 1, n (%)	35 (43)	77 (84)	< 0.001
At year 2, n (%)	57 (70)	80 (87)	0.013
At year 3, n (%)	59 (73)	81 (88)	0.019
At year 4, n (%)	59 (73)	85 (92)	0.001
At year 5, n (%)	63 (78)	82 (89)	0.069
Prolonged (year 1–5), n (%)	23 (28)	64 (70)	< 0.001
Clinical remission			
At year 1, n (%)	20 (25)	36 (39)	0.063
At year 2, n (%)	23 (28)	38 (41)	0.107
At year 3, n (%)	30 (37)	38 (41)	0.676
At year 4, n (%)	30 (37)	44 (48)	0.202
At year 5, n (%)	29 (36)	45 (49)	0.113
Prolonged (year 1–5), n (%)	13 (16)	23 (25)	0.208
Complete remission on treatment			
At year 1, n (%)	12 (15)	32 (35)	0.005
At year 2, n (%)	21 (26)	32 (35)	0.273
At year 3, n (%)	20 (25)	40 (44)	0.015
At year 4, n (%)	26 (32)	44 (48)	0.051
At year 5, n (%)	30 (37)	40 (44)	0.480
Prolonged (year 1–5), n (%)	8 (10)	19 (21)	0.082
Complete remission			
At year 1, n (%)	7 (9)	15 (16)	0.200
At year 2, n (%)	10 (12)	18 (20)	0.280
At year 3, n (%)	14 (17)	19 (21)	0.712
At year 4, n (%)	13 (16)	23 (25)	0.208
At year 5, n (%)	14 (17)	22 (24)	0.377
Prolonged (year 1–5), n (%)	4 (5)	8 (9)	0.502

SD: standard deviation.

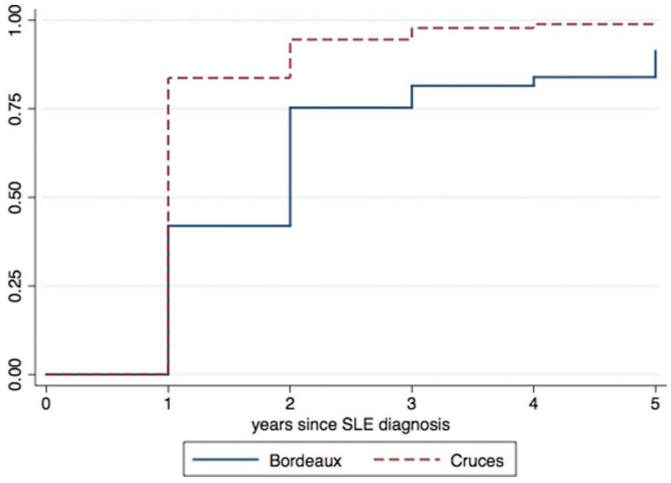

Fig. 3. Complete remission on treatment achievement over time.
Footnote:
BC: Bordeaux Cohort; CC: Cruces Cohort.

patients in CC vs. 11% in BC, p = 0.028, mainly to patients with mild-moderate disease at enrolment, i.e. with baseline SLEDAI < 12, (27% vs. 13%, p = 0.04). The difference was significant during each year of follow up (Fig. 2).

3.3. Analysis of remission

Overall, 112/173 patients (65%) achieved the main outcome (ClinROnT) at year one (early ClinROnT). Eventually, 165 patients (95%) reached ClinROnT, with 50% of patients having prolonged remission from year one to year 5. Patients on early ClinROnT were more likely to be on ClinROnT during the following 4 years (78% vs. 39%, p < 0.001).

Patients in CC achieved ClinROnT more frequently at all the pre-specified points of analysis (Table 2). The difference was more marked in early ClinROnT, 84% vs. 43% (p < 0.001). Prolonged ClinROnT was also more frequent among CC patients: 70% vs. 28%, p < 0.001.

In the survival analysis, achieving ClinROnT was significantly more likely in patients from CC (Fig. 3, p < 0.001, log-rank test). In the Cox regression, being in CC was a significant predictor of achieving ClinROnT after adjusting for baseline SLEDAI score (adjusted HR 1.69, 95%CI 1.21–2.35) or for baseline clinical manifestations (nephritis, neurological, cutaneous, articular, serosal and hematological, adjusted HR 1.72, 95% CI 1.2–2.4). Baseline SLEDAI score (adjusted HR 0.96, 95% CI 0.93–0.99) and neurological involvement (adjusted HR 0.39, 95% CI 0.16–0.91) were the only two negative predictors of achieving ClinROnT, with a trend for nephritis (adjusted HR 0.74, 95% CI 0.48–1.1, p = 0.15).

Table 2 shows the proportion of patients achieving the remaining types of remission during the 5 year follow-up. Differences were most marked at the 1st year. Prolonged ComROnT, ClinR and ComR were achieved by less of one quarter of patients in each cohort, with a trend for better outcomes in CC.

SLEDAI scores were similar in both cohorts during the follow-up, with mean values < 3 in all cases (Table 2).

3.4. Analysis of early clinical remission on treatment

Early ClinROnT was achieved more frequently in the CC irrespective of baseline SLEDAI score: 44/49 (90%) vs. 18/25 (72%), p = 0.049 in those with a SLEDAI 0–5; 28/33 (85%) vs. 15/43 (34%), p < 0.001 in those with a SLEDAI 6–12; and 5/10 (50%) vs. 2/13 (15%), p = 0.07 in those with a SLEDAI > 12.

Likewise, early ClinROnT was achieved more frequently in the CC among those presenting with cutaneous involvement, 56/68 (82%) vs. 24/57 (42%), p < 0.001; articular involvement, 51/62 (82%) vs. 30/73 (41%), p < 0.001; nephritis 8/15 (53%) vs. 3/14 (21%), p = 0.07; or with CNS involvement, 3/3 (100%) vs. 0/6 (0%), p = 0.012. No significant differences were seen among patients presenting with serositis or with hematological manifestations (thrombocytopenia or hemolytic anemia).

Early ClinROnT was more likely in CC after adjusting for baseline SLEDAI score (adjusted OR 7.1, 95%CI 3.3–15.6) and for baseline clinical manifestations (nephritis, neurological, cutaneous, articular, serosal and hematological, adjusted OR 6.9, 95% CI 3.1-15-5). Baseline SLEDAI was an adverse predictor for early ClinROnT (adjusted OR 0.84, 95%CI 0.78–0.91). Nephritis (adjusted OR 0.17, 95%CI 0.06–0.44) and neurological involvement (adjusted OR 0.2, 95%CI 0.04–1.02) were the only two baseline negative predictors of early ClinROnT.

4. Discussion

SLE is a multisystemic disease with protean clinical manifestations in which the concept of activity and remission is somehow difficult to characterise. Despite the availability of a number of activity scales, there is no full agreement on what a lupus flare is [22]. Moreover, remission cannot be considered just the absence of clinically apparent activity, given the potential for long-term complications of both low-grade inflammation and immunosuppressive therapy. In other words, remission can not be maintained at any price; this is particularly true for glucocorticoids, a well established cause of irreversible organ

Table 3
Remission studies.

Authors, year [ref.]	N	Inception (yes/no)	Remission definitios		Treatment allowed	Remission achieved (%)					
Steiman, et al. 2014 [7]	1613	No	SLEDAI-2 K = 0, = 2 or = 4 (based on serology) for ≥5 years		AM, GC and/or IS	2.1					
					AM	2.4					
Zen, et al. 2015 [27]	224	No	cSLEDAI-2 K = 0 for ≥5 years								
			Three levels:	Clinical remission on-GC	AM, IS, GC ≤5 mg/d	15.6					
				Clinical remission off-GC	AM, IS	14.7					
				Complete remission[a]	AM	7.1					
Zen, et al. 2017 [10]	293	No	cSLEDAI-2 K = 0 for 1, 2, 3, 4 and ≥ 5 consecutive years			1 year	2 years	3 years	4 years	≥5 years	
			Three levels:	Clinical remission on-GC	AM, IS, GC ≤5 mg/d	7.5	11.6	8.6	4.1	12.3	
				Clinical remission off-GC	AM, IS	1.0	3.7	5.8	4.5	17.1	
				Complete remission[a]	AM	0.7	0.7	1.0	0.3	9.2	
Wilhelm, et al. 2016 [28]	2307	No				Time in remission					
			DORIS criteria [8] estimating the time to remission and the time from remission to relapse			1 year	2 years	5 years	10 years		
			DORIS definitions [8]:	Clinical ROT	AM, IS, GC ≤5 mg/d	13.4	5.6	0.6	0.3		
				Complete ROT[a]	AM, IS, GC ≤5 mg/d	9.3	3.6	0.7	0.7		
				Clinical remission	AM	13.2	5.6	1.2	0.4		
				Complete remission[a]	AM	12.1	5.2	2.0	1.3		
Tsang-A-Sjoe, et al. 2016 [26]	183	No	LLDAS [9] and Remission [10] for 1, 2, 3, 4 and ≥ 5 consecutive years			1 year	2 years	3 years	4 years	≥5 years	
			Clinical remission on-GC		AM, IS, GC ≤5 mg/d	14.2	13.6	10.2	11.3	11.1	
			Clinical remission off-GC		AM, IS	23.0	25.4	30.6	29.2	37.6	
			Complete remission[a]		AM	17.5	16.6	20.4	12.3	12.8	
			Consecutive years in remission (any of the above)		Any of the above	54.6	43.8	39.6	33.0	32.5	
			LLDAS		AM, IS, GC ≤7.5 mg/d	56.2	40.2	33.3	20.8	16.2	
Ugarte-Gil, et al. 2017 [21]	1350	No	Four disease activity statuses, analysing the median number and length of intervals per patient			Best	Last				
			Remission on-therapy (SLEDAI =0)		AM, GC ≤5 mg/d and/or IS	16.5	10.4				
			Remission off-therapy (SLEDAI =0)		AM	3.7	1.9				
			LDAS [21] (SLEDAI ≤4)		AM, GC ≤7.5 mg/d and/or IS (m)	14.2	11.0				
			Non-optimally controlled status (SLEDAI > 4)		AM and/or GC > 7.5 mg/d and/or IS	65.6	76.6				
Tani, et al. 2018 [25]	115	No	LLDAS [9] and Doris [8] criteria at baseline and during 4 years			Baseline	year 1	year 2	year 3	year 4	sustained
			RONT		AM, IS, GC ≤5 mg/d	49.6	46.0	52.1	47.8	47.8	21.7
			Complete RONT[a]		AM, IS, GC ≤5 mg/d	28.7	26.0	26.9	19.1	20.8	7.8
			ROFT		AM	10.4	12.1	15.6	20.0	20.0	5.2
			Complete ROFT[a]		AM	1.7	3.5	6.9	6.9	7.8	0.8
			LLDAS5 [25]		AM, IS, GC ≤5 mg/d	61.6	60.0	70.2	68.1	73.9	35.6
			LLDAS		AM, IS, GC ≤7.5 mg/d	63.1	63.1	70.2	68.1	74.8	36.5

cSLEDAI, clinical SLEDAI (Systemic Lupus Disease Activity Index); GC, glucocrticoids; AM, antimalarials; IS, immunosuppresives; DORIS, Definitions Of Remission In SLE; ROT and RONT, Remission on treatment; ROFT, remission of treatment.

[a] Complete remission requieres negative serology (anti-dsDNA and complement C3, C4); LLDAS, Lupus Low Disease Activity State. Defined by the Asia-Pacific Lupus Collaboration [9]; LDAS, Low Disease Activity State. Defined by the GLADEL [21]; LLDAS5, LLDAS with a glucocorticoid dosage ≤5 [25].

damage in lupus when given at doses > 7.5 mg/d [23] or even less [24].

Taking this into account, consensus documents have defined remission criteria with clinical implications. ClinROnT according to DORIS definitions [8] and LDA [9] are similar concepts, although the former is somewhat more restrictive, not allowing activity at any SLEDAI clinical item (in LDA non-major organ systems can be active) and not permitting any dose of prednisone > 5 mg/d (> 7.5 mg/d in LDA). The remaining DORIS definitions for remission are even more restrictive. Complete remission of any kind (with or without treatment) requires of an SLEDAI score = 0 as an entry criteria. For a patient to be in ClinR no glucocorticoids or immunosuppressive drugs are allowed. While ClinR, ComR and ComROnT are difficult to achieve, both ClinROnT and LDA have been demonstrated realistic goals and associated with decreased damage accrual [25,26].

The two cohorts included in this study enrolled inception patients with SLE. Despite the similar demographic and clinical profile, the therapeutic approach was patently different: pulses of methyl-prednisolone, HCQ and methotrexate were used more frequently in the CC, a fact that allowed a concomitant reduction in the amount of oral prednisone, both maximum and average daily doses, during each year of follow-up. > 95% of patients in CC took ≤5 mg/d of prednisone at each yearly study point.

This difference actually influenced the remission rates in both cohorts: whilst the reduction in SLEDAI scores was very similar, more patients in CC achieved ClinROnT at every study point, particularly at year one (84% vs. 43%), when the difference in patients on prednisone ≤5 mg/d was also more marked (97% vs. 44%). In other words, patients in CC achieved a similar reduction in activity using much lower doses of oral prednisone, which were at the ≤5 mg/d security threshold [23] in virtually all patients very early after the diagnosis of SLE.

Results of previous studies on this topic are summarised on Table 3. Comparisons are often difficult to make, since different definitions of remission have been used, and also because some studies segregated patients on clinical remission not taking any steroids from those fulfilling criteria for ClinROnT. However, it is clear that any form of complete remission (i.e. with normal serology) was rare. Sustained clinical remission, the equivalent of our definition for prolonged ClinROnT, was achieved, at best, by < 35% of patients. Moreover, patients entered most studies either in remission or with mean SLEDAI scores < 4 [25], and, in those enrolling active patients, remission rates were much lower [28].

This is the first study in which only inception patients were included. Mean SLEDAI scores at enrolment were > 6 in both cohorts, expectedly higher than those seen in previous non-inception cohorts. Despite this fact, prolonged ClinROnT was achieved in BC in a similar proportion of those previously described (28%) and in 70% patients of CC. Indeed, > 80% and 50% of patients of CC with a presenting SLEDAI 6–12 and > 12, respectively, were in ClinROnT by the end of the 1st year. Patients of BC exhibited lower remission rates in the 1st year, however, after the 2nd year figures were over 70% (Table 2).

These differences between both cohorts are likely explained by the different therapeutic approach. Both HCQ and methotrexate have been linked to keeping SLE under remission in randomised clinical trials [29,30]. Virtually all patients in CC were treated during the 5 years of follow-up with HCQ; in the BC, HCQ was ever given to 91% of patients, but only 73% were taking the drug at the end of the follow-up. This resulted in > 13 extra months of HCQ therapy in patients from CC. The proportion of patients on HCQ was < 75% in most previous cohorts [25,26,28]. Methotrexate was given to 24% of CC patients, compared with 11% in BC. Pulse methyl-prednisolone has been shown to speed up remission in patients with moderate-severe renal [31] and non-renal SLE [14,32], and were used much more frequently in patients of CC. Of note, the differences in the use of methotrexate and pulse methyl-prednisolone were mainly seen among patients presenting with mild-moderate disease. In other words, patients within CC with non severe disease were often treated with combination therapy, resulting in a more rapid and sustained remission in the setting of a markedly reduced amount of oral prednisone.

The most important limitation of this study is that remission was assessed at fixed yearly points, so potential flares between visits were not recorded. It is thus possible that a proportion of patients categorised as being in prolonged remission were actually not. However, if that was the case, flares were easily controlled so remission could be attained by the next yearly visit with prednisone dose back to ≤5 mg/d. Also, more the 90% patients were Caucasians with full access to public health facilities.

In summary, this study shows that prolonged ClinROnT, a validated outcome protective against damage accrual, is an achievable goal by using lower doses of oral prednisone. This could be accomplished by means of universal HCQ therapy, frequent pulse methyl-prednisolone (usually 125 or 250 mg/d) in patients with severe but also moderate disease activity and methotrexate in a substantial number of patients with mild-moderate activity. The long-term implications and the individual predictors of favourable outcomes deserve further investigation in future studies.

Declaration of Competing Interest

The authors declare that they have no competing interest.

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