Clinical Trials

CT-01 ASSOCIATION BETWEEN HYDROXYCHLOROQUINE NON-ADHERENCE AND DISEASE ACTIVITY IN A PREDOMINANTLY HISPANIC SYSTEMIC LUPUS ERYTHEMATOSUS COHORT

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Background Hydroxychloroquine (HCQ) is a key component of therapy for Systemic Lupus Erythematosus (SLE). Medication non-adherence is reported in 40%–80% of lupus patients and results in increased morbidity, mortality, and health care utilization. HCQ levels are a sensitive and reliable method to assess medication adherence. Our study evaluated the feasibility of HCQ level measurement in a routine clinical setting and its association with disease activity in a predominantly Hispanic population.

Abstract CT-01 Table 1 Patient characteristics by adherence status

	HCQ level<500 (n=44)	HCQ level≥500 (n=64)	p value
Socio-Demographics			
Age, years	38 (19–64)	38 (20–66)	0.867
Female	40 (91)	58 (91)	1.0
Race/Ethnicity			
White	4 (9)	11 (17)	0.254
Hispanic	30 (68)	37 (58)	0.214
African American	9 (21)	12 (19)	0.985
Other	1 (2)	4 (6)	0.350
Primary Language, n (%)	(n=40)	(n=60)	
Spanish	13 (32)	15 (25)	0.174
Literacy score, mean (range)	3.1 (0–6), n=28	2.9 (0–6), n=40	0.623
Household income <$15,000,	21 (70), n=30	29 (58), n=50	0.551
Education	n=34	n=53	
Did not complete high school	6 (18)	10 (19)	0.210
SLE and Additional Characteristics			
Disease Duration, years	9 (1–35)	9 (1–29)	0.985
Organ Involvement, n (%)	28 (64)	31 (48)	0.147
Lupus Nephritis	20 (45)	19 (30)	0.127
CNS	1 (2)	9 (14)	**0.041**
SLEDAI-2K	5.7 (0–20)	3.2 (0–15)	**<0.001**
SLICC SDI	0.97 (0–4)	0.76 (0–5)	0.400
Use of steroids in past month, n (%)	24 (55)	30 (47)	0.507
Current use of immunosuppressant agent, n (%)	30 (68)	38 (59)	0.498
Smoker, n (%)	4 (9)	6 (9)	0.990
eGFR, mean (range)	58 (30–60)	54.5 (4–60)	0.116
Weight, mean kg (range)	73.5 (34.6–121)	70.9 (30–115)	0.432
Diagnosis of Depression	16 (36)	14 (22)	0.055

Methods SLE patients from the Columbia University Lupus cohort, treated with HCQ for ≥6 months and reporting medication-adherence were included. HCQ levels were measured by whole blood high performance liquid chromatography. Non-adherence was defined as HCQ level <500 ng/ml. Univariable and multivariable regression models were constructed to evaluate the association between HCQ level and disease activity measured by SLEDAI-2K.

Results One-hundred and eight patients were enrolled (table 1); the mean age was 38 years, 91% were female, and 62% were Hispanic. The average SLEDAI-2K was 4.3 (0–20). Forty-one percent of patients had HCQ levels<500 ng/ml consistent with non-adherence, of whom 19% had undetectable levels. A higher SLEDAI-2K score was associated with low HCQ levels ($p<0.001$). This association remained significant after adjusting for age, sex, race/ethnicity, education, primary language, glomerular filtration rate, depression, smoking, major organ involvement, steroid use, and immunosuppression ($p<0.004$).

Conclusions HCQ levels <500 ng/ml were associated with higher disease activity and accounted for 32% of the SLEDAI variability. HCQ levels are a simple and reliable method to evaluate medication adherence in SLE. Levels <500 ng/ml should be discussed with patients and the reasons for non-adherence should be further explored and addressed.

Acknowledgements We acknowledge the patients who participated in this study.

CT-02 KIDNEY BIOPSY FINDINGS OF LUPUS NEPHRITIS PATIENTS IN REMISSION AND RENAL FLARE AFTER WITHDRAWAL OF MAINTENANCE THERAPY: A PROSPECTIVE OBSERVATIONAL COHORT STUDY

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Background One of the most difficult management issues in lupus nephritis (LN) is duration of maintenance immunosuppression after patients are in clinical remission. Most patients receive immunosuppression for years, based mainly on expert opinion. Prospective data are unavailable. Complicating this issue are data that patients in clinical remission can still have histologically active LN, however the implications of this are unknown. The Lupus Flares and Histological Renal Activity at the end of Treatment (LuFla) study was designed to examine whether residual histologic activity predisposes to LN flares in class III and IV LN.

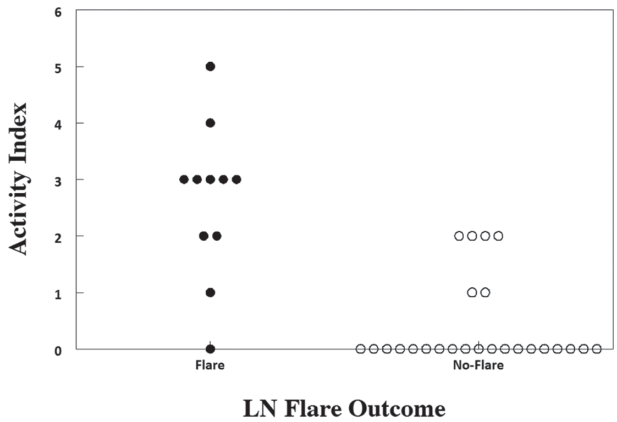
Methods Patients in complete clinical remission for at least 12 months who had received at least 36 months of immunosuppression were eligible. Patients consented to a second kidney biopsy and were then tapered off maintenance immunosuppression. The patients were followed prospectively for LN flares over 24 months.

Results LuFla enrolled 44 patients and 36 completed the study. LN flares occurred in 11 patients (30.5%) and 10 (90.9%) of these had residual histologic activity on biopsy 2 (figure 1). All patients with an NIH activity index (AI)>2 flared (figure 1). Endocapillary proliferation, a component of the AI and duration of SLE at biopsy 2 were independent predictors of flare. A predictive equation based on these variables discriminated between flare and no-flare with a sensitivity of 100%, specificity of 92%, and a misclassification rate of 5.6%.

Conclusions These data suggest a repeat kidney biopsy is useful in managing maintenance immunosuppression in LN, and

patients in histologic remission are candidates for withdrawal of therapy.

Trial registration ClinicalTrial. gov, NCT02313974



Abstract CT-02 Figure 1 Persistent histologic activity on repeat biopsy after clinical remission is associated with renal flare after withdrawal of maintenance immunosuppression

CT-03 PHASE 2 TRIAL OF INDUCTION THERAPY WITH ANTI-CD20 (RITUXIMAB) FOLLOWED BY MAINTENANCE THERAPY WITH ANTI-BAFF (BELIMUMAB) IN PATIENTS WITH ACTIVE LUPUS NEPHRITIS

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Background Despite case series suggesting efficacy, controlled trials of anti-CD20 in lupus nephritis (LN) did not confirm benefit (*Arthritis Rheum* 2012;64:1215 and 2013;65:2368).

Objectives One possible explanation for this failure stems from the fact that B cell depletion stimulates production of B cell activating factor (BAFF) which, in turn, facilitates maturation of autoreactive B cells in lymphoid organs or during B cell repopulation. The CALIBRATE study (NCT 02260934) was designed to test this hypothesis, to determine whether addition of anti-BAFF could enhance the clinical effects of anti-CD20, and to assess safety of the combination.

Methods Forty-three patients with active LN despite conventional treatment enrolled in a prospective randomized open-label trial that compared two treatment strategies. All subjects received iv rituximab (1000 mg), CTX (750 mg), and methylprednisolone (100 mg) at wks 0 and 2, followed by 40 mg/d prednisone tapered to 10 mg/d by wk 12. At wk 4, subjects received either belimumab (10 mg/kg iv at wks 4, 6, 8 and then every 4 wks) plus prednisone (n=21) or prednisone alone (n=22). Complete response (CR) was defined as: (i) urine protein:creatinine ratio (UPCR) <0.5; (ii) eGFR >120 or, if <120, eGFR >80% of screening; and (iii) prednisone tapered to 10 mg/d. The definiton of partial response (PR) differed only in the UPCR criterion (>50% reduction).

Results The clinical outcome at wk 24 was similar in both groups (table 1). The CR rate was 24% in the belimumab group (RCB) and 23% in the control group (RC). Three subjects in each group withdrew (WD) prior to wk 24 (two withdrawals in each group due either to progressive nephritis or an infusion reaction, and one in each group for reasons unrelated to SLE or its treatment). B cell depletion from blood was virtually absolute in both groups at wk 12, but the pace of recovery differed. Six subjects experienced serious adverse events between wks 0 and 24; three subjects in the RC group (pneumonia followed by LN flare; deep vein thrombosis; SLE flare); and three subjects in the RCB group (anti-CD20 infusion reaction; soft-tissue abscesses prior to anti-BAFF treatment; quadriceps tendon rupture).

Conclusions An interim analysis of data from CALIBRATE shows: (i) anti-BAFF following anti-CD20 for LN did not improve clinical outcome at week 24; (ii) anti-BAFF delayed blood B cell reconstitution following B cell depletion; and (iii) anti-BAFF following anti-CD20 was not associated with hypogammaglobulinemia or an increase in serious infections. Further analyses at 48 weeks and beyond will address how anti-BAFF therapy affects quantitative and qualitative recovery of B cells as well as long-term clinical outcome.

Abstract CT-03 Table 1

					Median B Cell Count			Median IgG Level	
	CR	PR	NR	WD	Wk0	Wk12	Wk24	Wk0	Wk24
RC Group	23%	23%	41%	14%	105	1	31	1050	1100
RCB Group	24%	24%	38%	14%	143	1	3	984	837

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CT-04 SAFETY AND EFFICACY OF ALLOGENEIC UMBILICAL CORD-DERIVED MESENCHYMAL STEM CELLS (MSCS) IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: RESULTS OF AN OPEN-LABEL PHASE I STUDY

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Background Mesenchymal stem cells (MSCs) are known to possess significant immunosuppressive properties, and their use in refractory SLE is supported by promising safety and efficacy in autoimmune animal models and human trials. We conducted this phase I open-label study to test the hypothesis that a single infusion of human allogeneic umbilical cord-derived MSCs (IND 16377) is safe when added to standard-of-care therapy for active SLE. The primary safety outcome is frequency of Grade 3 or higher adverse events (AEs) by Week 24. The primary efficacy outcome is change in SLE disease activity between Baseline and Week 24 measured by SLEDAI score and prednisone dose.