SAT0247 EFFICACY AND SAFETY OF MODIFIED-RELEASE PREDNISONE IN MANAGING MODERATE ACTIVITY SYSTEMIC LUPUS ERYTHEMATOUS DURING PREGNANCY: AN IMPLEMENTED CASE-CONTROL STUDY

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Background: Systemic lupus erythematosus (SLE) primarily affects women of childbearing age. Despite the overall favorable outcome, pregnancy represents a challenge for both patients and clinicians. Since the complications rate is linked to the disease activity, the achievement of remission is recommended before pregnancy. Prednisone represents a cornerstone in SLE management and is safely used, at low doses (<7.5 mg daily), during pregnancy. Modified-release prednisone (MRP) optimize corticosteroid treatment strategy in rheumatic diseases, thanks to its capability of respect the physiological cortisol circadian secretion. MRP has been approved from FDA in SLE treatment, but no data are available regarding its administration during pregnancy.
Objectives: We aimed to investigate whether this drug is safe and effective as the immediate release prednisone (IRP) in SLE pregnant patients.
Methods: We retrospectively evaluated 9 female patients, fulfilling the ACR criteria for SLE, consulting our Centers in a 4-years observational range. All of them, thanks to a stable disease (not requiring treatment regimen modifications within 12 months), experienced a successful pregnancy during the observation. All the cases were taking low-dose MRP (5 to 7.5 mg/daily) as a baseline treatment, from at least 6 months. They were matched to 9 controls, defined as SLE patients with the same age and duration of disease, taking the same prednisone dose, from at least 6 months, in the IR formulation. Overall pregnancy outcome features; SLE disease activity (calculated at least once during pregnancy, SLEPDAI) and at baseline/post-partum (SLEDAI) score; patient's global assessment (VAS) at baseline, during pregnancy and in postpartum (mm); need of treatment changes throughout pregnancy and at postpartum (%) were assessed. Homogeneity tests, percentages and scores comparison were run out by non-parametric statistical analysis.
Results: Mean MRP age group was 26±7; disease duration, 4±8 years; IR one, respectively, 28±6 and 3±9 (both, p=ns). SLEDAI at baseline was 1±0.1 among MPR and 1±0.3 among IR women; SLEPDAI, 1±0.9 and 2±0.2 (both, p=ns). No major perinatal complications were detected. Preterm births, cesarean section rates, newborns weight and APGAR scores did not differ between the two subpopulations (all, p=ns). SLEDAI assessed at postpartum was 2.8±0.6 in MRP subjects and 3.4±0.4 in IR (p<0.05). Patients VAS (MRP *vs* IR) was 3±0.4 and 2±09 at baseline (p=ns); 2±0.6 and 4±0.7 during pregnancy (p<0.05) and 3±0.3 and 4±0.9 at postpartum (p<0.05). Regarding treatment regimen changes (add-on strategy), the observed rates involved 1/9 (MRP) and 5/9 (IR) women during the observational gap (pregnancy+postpartum) (p<0.001). Results synthesis is reported in Table I.

	Cases MRP	P value	Controls IRP
Age (years±months)	26±52	ns	28±43
Disease duration (years±months)	4±8	ns	3±9
PDN dose baseline (mg)	5±2.5	ns	5±2.5
SLEDAI baseline	1±0.1	ns	1±0.3
VAS baseline (mm)	20±6	ns	21±5
PDN dose pregnancy (mg)	5±2.5	p<0.05	7.5±2.5
SLEPDAI	1±0.9	p<0.05	3±0.2
VAS pregnancy (mm)	41±8	p<0.05	23±7
Gestation (weeks±days)	38±5	ns	37±6
Child weight (g)	3230±420	ns	3120±390
APGAR	9±1	ns	9±0
PDN dose postpartum (mg)	2.5±2.5	p<0.05	5±2.5
PDN need to change (%)	11	p<0.001	56
SLEDAI postpartum	2.8±0.6	p<0.05	3.4±0.4
VAS postpartum (mm)	50±4	p<0.05	71±6

Conclusions: Activity (SLEDAI) score was significantly higher at postpartum and treatment had to be increased in IR patients, in comparison to the MRP, to manage SLE. VAS, conversely, was significantly higher among IR, both during pregnancy and postpartum. No major perinatal side effects were observed during the study; minor and expected complications rates did not differ between the two subpopulations. Despite the limited number of subjects, MRP treatment seems to be as safe, but more effective, in comparison to the standard IR one, during pregnancy of SLE-affected women.
Disclosure of Interest: None declared
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SAT0248 BASELINE CLASI-DAMAGE IS A MAJOR PREDICTOR OF SKIN RESPONSE TO BELIMUMAB IN A MULTICENTRIC COHORT OF SLE PATIENTS

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Background: Belimumab is used to treat several systemic lupus erythematosus (SLE) manifestations and predictors of response are advisable in clinical practice.
Objectives: To explore the effects of belimumab treatment on skin involvement in SLE patients in a real-life setting.
Methods: SLE patients treated with belimumab (10 mg/kg day 0, 14, 28 and then every 28 days), as add-on therapy in 11 Italian cohorts were prospectively followed-up for 24 months. Skin involvement was measured by the CLASIa score (Cutaneous Cutaneous LE Disease Area and Severity Index Activity) at baseline and every six months until month 24. Damage was measured by CLASI-Damage (CLASId). Response was defined as CLASIa <2 at measured timepoints.
The following variables were tested to determine baseline predictors of response at 12, 18 and 24 months: gender, age, disease duration, SLE activity index 2000 (SLEDAI-2K) ≥10, prednisone dose >7.5 mg/day, baseline CLASIa and CLASId, concomitant immunesuppressants (yes/no) and number of previous immunesuppressants. Statistical analysis was performed with SPSS 22.0 software.
Results: 188 patients were studied, among whom 48 (25.5%) had skin involvement as the leading feature for belimumab therapy. Mean follow-up period was 17.5±10.96 months. Thirty-eight patients completed a 6-month follow-up; 27 completed a 12-month follow-up; 19 completed a 18-month follow-up and 15 completed a 24-month follow-up. Fourteen patients discontinued due to adverse events (7/14, 50%), lack of efficacy (4/14, 28.5%) or other causes (3/14, 21.4%). CLASIa, daily prednisone dosage and SLEDAI-2K significantly decreased during the follow-up (p<0.001). CLASIa<2 was achieved by 25/38 patients (65.7%) at 6 months, 19/27 (70%) at 12 months, 11/19 (58%) at 18 months and 10/15 (67%) at 24 months. A lower baseline CLASIa was associated with CLASIa response at 18 and 24 months (responders vs. non-responders: 3.4±2.4 vs. 9.5±5.6; 3.5±2.5 vs. 11.2±6.5; p<0.005 for both), while a lower baseline CLASId was associated with CLASIa response at each timepoint (responders vs. non-responders: at 12 months: 0.6±0.9 vs. 2.4±2.5; at 18 months: 0.5±0.8 vs. 2.5±2.3; at 24 months: 0.6±0.8 vs. 3.25±2.7; p=0.01 for all). Multivariate analysis was only performed at 12 months due to low patient number at 24 months. CLASId was the only independent negative predictor of response (OR 0.52, p=0.05). Notably, CLASId remained stable during the follow-up.
Conclusions: Belimumab use in cutaneous involvement is associated with reduced activity in skin lesions and hindrance of skin damage. Early use of belimumab before damage is established is likely to be associated with a better response.
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SAT0249 SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND INHIBITION OF T-CELL DEPENDENT ANTIBODY RESPONSE (TDAR) WITH MEDI4920, A NOVEL, ENGINEERED CD40 LIGAND (CD40L) ANTAGONIST: RESULTS OF A FIRST-TIME-IN-HUMAN STUDY

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Background: The CD40/CD40L pathway is involved in the T-cell-dependent activation of B cells, which subsequently produce autoantibodies and inflammatory mediators that contribute to autoimmune disease pathology. MEDI4920 is an engineered fusion protein and antagonist of CD40L that lacks the fragment crystallisable (Fc) domain thought to be involved in thromboembolic events (TEs) previously reported with anti-CD40L agents containing an Fc domain.
Objectives: The primary objective of this Phase I, randomised, double-blind, placebo-controlled, single-ascending dose study was to evaluate the safety and tolerability of MEDI4920 in healthy subjects. Secondary objectives were to characterize T-cell-dependent antibody response (TDAR) to keyhole limpet hemocyanin (KLH) neoantigen, pharmacokinetics (PK), and anti-drug antibodies (ADAs) to MEDI4920.
Methods: Fifty-six healthy adult male subjects, aged 19–49 years, received a single intravenous dose of either MEDI4920 (3, 10, 30, 100, 300, 1000 or 3000 mg) or placebo. TDAR inhibition was analysed by measuring serum concentrations of

IgG and IgM antibodies to KLH over time. A dose–response model was generated for TDAR inhibition. Blood samples were collected to evaluate PK, total soluble CD40L (sCD40L) and ADA concentrations.

Results: No deaths, TEs, severe or serious hypersensitivity reactions or infections or infusion-related reactions were observed in the study. One serious adverse event (fractured tibia) was reported in the placebo arm. MEDI4920 showed inhibition of the TDAR IgG response after the second administration of KLH on Day 15 at higher doses (≥300 mg; Figure 1A). An E_{max} model adequately characterised the TDAR dose–response at Day 43 ($p<0.001$; ED_{50}=491 mg), with the 3000 mg dose showing 86% inhibition of the TDAR (95% CI: 68–94%; Figure 1B). MEDI4920 exhibited linear PK. MEDI4920 produced a dose-dependent increase in total sCD40L concentrations. A high ADA incidence (90%) was observed in dose cohorts ≤100 mg; however, ADA incidence (29%) and ADA titres decreased with ≥300 mg doses of MEDI4920. ADA-high subjects had reduced MEDI4920 and total sCD40L concentrations compared with ADA-negative subjects or those with low ADA titres. ADA incidence did not correlate with any clinical events.

Figure 1A: Plot of mean anti-KLH IgG concentrations over time

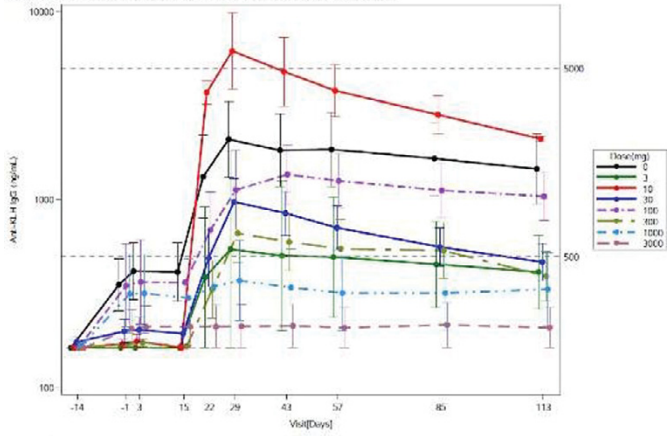
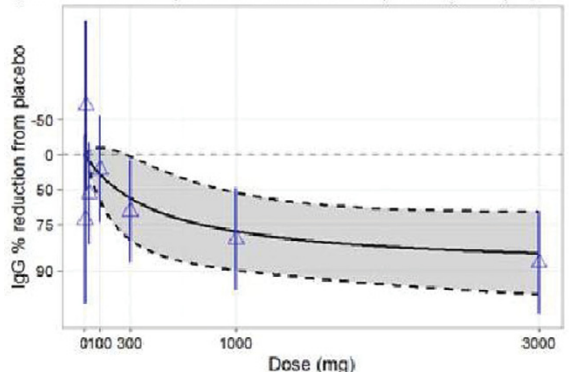


Figure 1B: Plot of dose–response model for TDAR inhibition (anti-KLH IgG at Day 43)



Conclusions: MEDI4920 demonstrated an acceptable safety and tolerability profile, and dose-dependent inhibition of TDAR. The dose-dependent increase in total sCD40L concentrations indicates binding of MEDI4920 to sCD40L and target engagement. The decreases in ADA incidence and ADA titres correlate with increasing MEDI4920 dose, consistent with the immunosuppressive mechanism of action of this molecule. These results support further exploration of MEDI4920 administration in subjects with autoimmune diseases where the CD40/CD40L pathway is activated.

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SAT0250 BODY MASS INDEX IS INVERSELY ASSOCIATED WITH RESPONSE TO RITUXIMAB IN LUPUS NEPHRITIS: ANALYSIS OF THE LUNAR TRIAL

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Background: Increased body mass index (BMI) has been associated with poor functional capacity and systemic inflammation in lupus,[1] alterations in rituximab (RTX) pharmacokinetics,[2] and failure to achieve trial endpoints among patients treated with RTX for ANCA-associated vasculitis.[3] Although RTX is not approved for the treatment of lupus nephritis (LN), current EULAR/ERA-EDTA guidelines include RTX for use in refractory cases.[4] The effect of BMI on outcomes of patients treated with RTX for LN is unknown.

Objectives: To assess the association between pre-treatment BMI and renal response using data from the LUNAR trial.

Methods: LUNAR randomized 144 patients with ISN/RPS class III or IV LN to RTX (2 doses of 1000 mg at baseline and month 6) or placebo in combination with mycophenolate and a steroid taper.[5] BMI was measured at the screening visit. Complete renal response (CRR) was defined as achievement of UPCR <0.5, normal serum creatinine not increased from baseline by >15%, and inactive urinary sediment at week 52. Alternative definitions of response and achievement of CRR at week 78 were also considered. Logistic regression was used to model interactions and to calculate odds ratios (OR) and 95% CI. Peripheral $CD19^+$ B cell measurements were examined.

Results: We identified qualitative interactions between BMI and treatment for CRR and alternative response measures. In unadjusted analysis, each 5 kg/m^2 increase in pre-treatment BMI was associated with OR =0.47 (95% CI 0.24–0.92) in the RTX group and OR =1.44 (95% CI 0.93–2.23) in the placebo group for achievement of CRR (*P* value for interaction =0.006). The results of analysis adjusted for baseline UPCR and serum creatinine are presented in the Table. A sensitivity analysis identified consistent associations between BMI and response in the RTX group only. Among patients in the RTX group, increased BMI was associated with increased time to peripheral $CD19^+$ count <5 cells/μL (Figure).

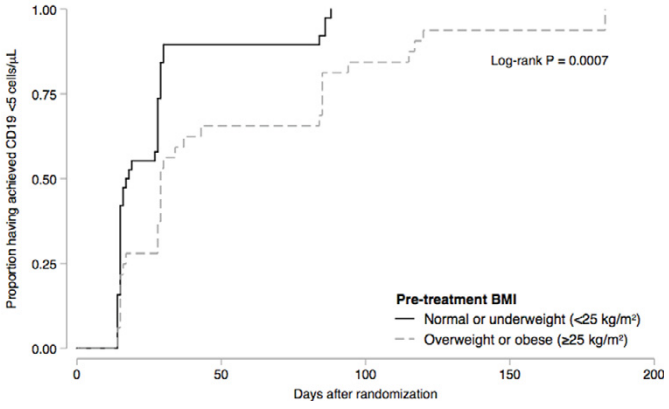
Table 1

	Adjusted OR (95% CI) per 5 kg/m^2 increase in pre-treatment BMI		*P* value for interaction
Response measure	Rituximab (n=72)	Placebo (n=72)	
CRR	0.48* (0.23–0.97)	1.60* (1.01–2.55)	0.005
Overall renal response	0.78 (0.51–1.19)	1.42 (0.94–2.16)	0.045
UPCR <0.5	0.61* (0.38–0.97)	1.37 (0.91–2.07)	0.010
UPCR <0.7	0.58* (0.37–0.92)	1.33 (0.87–2.02)	0.010
CRR at week 78	0.53* (0.29–0.99)	1.58 (0.99–2.52)	0.006

*P <0.05.

All endpoints were measured at week 52 except where specified.

Figure. Kaplan-Meier estimates: Time to peripheral $CD19^+$ count <5 cells/μL



Conclusions: In this exploratory analysis of the LUNAR trial, BMI was inversely associated with renal response among patients treated with RTX. We did not observe this same relationship between BMI and response among patients in the placebo group, and in fact found evidence of a positive correlation between BMI and one measure of response in this group. Among patients treated with RTX, BMI was associated with time to B cell depletion, generating the hypothesis that the observed differences in response are mediated by differences in the timing and/or degree of B cell depletion. These findings warrant additional analyses to better understand the relationships between patient characteristics, pharmacokinetics, B cell depletion, and treatment response in the LN population.

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