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SAT0221 SIX-MONTH PROTEINURIA MEASUREMENT PREDICTS RENAL RESPONSE AT 18 MONTHS IN LUPUS NEPHRITIS: ANALYSIS OF TWO PHASE III RANDOMIZED CLINICAL TRIALS

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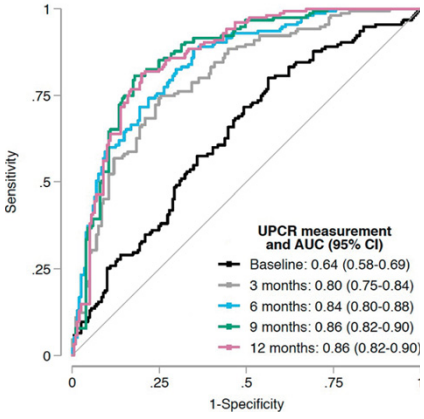
Background: Early identification of patients with lupus nephritis (LN) likely to achieve complete renal response (CRR) may expedite the evaluation of new therapies and guide clinical care. Prior analyses have shown that early improvement in proteinuria is associated with subsequent renal response.[1,2] Several ongoing LN trials including NOBILITY, an assessment of the efficacy of the anti-CD20 monoclonal antibody obinutuzumab in combination with standard of care immunosuppression, will evaluate proteinuric response at 6 months as a key secondary endpoint.[3] Whether short-term response accurately predicts future CRR, however, is uncertain.
Objectives: To assess the predictive value of early measurements of the level of proteinuria and to identify proteinuria cutoffs that best identify patients who will achieve CRR at 18 months.
Methods: LUNAR and BELONG were multicenter, double-blinded studies that in total randomized 522 patients with ISN/RPS class III or class IV LN to blinded investigational infusions or placebo in combination with standard of care immunosuppression.[4,5] CRR was assessed at 18 months and defined for this analysis as achievement of urine protein to creatinine ratio (UPCR) <0.5 with normal serum creatinine that was not increased from baseline by $>25\%$. Bootstrapping was used to generate nonparametric receiver operating characteristic (ROC) curves and estimate area under the curve (AUC). The Youden index was used to identify UPCR cutoff values that maximize sensitivity and specificity. Positive predictive value (PPV) and negative predictive value (NPV) were calculated.
Results: ROC curves were constructed for proteinuria measurements at baseline and 3, 6, 9, and 12 months after randomization (Figure 1). AUC increased from baseline to month 3 (0.64 vs. 0.80, $P<0.001$) and from month 3 to month 6 (0.80 vs. 0.84, $P<0.01$) but did not increase beyond month 6 ($P>0.05$ for each pairwise comparison). Achievement of 6-month UPCR <1 was 83.8% sensitive and 71.0% specific for CRR at 18 months and had PPV and NPV of 64.9% and 87.2%, respectively. Evaluation of lower 6-month UPCR cutoff values yielded improvements in specificity and PPV but marked decreases in sensitivity and NPV. In multivariate analysis, the addition of 6-month serum creatinine and percent change in UPCR from baseline did not result in meaningful increases in AUC compared with 6-month proteinuria measurement alone.

Figure: Receiver operating characteristic curves for CRR at 18 months



Conclusions: Level of proteinuria at 6 months alone was predictive of CRR at 18 months in aggregated data from two phase III LN clinical trials. After 6 months of treatment, UPCR <1 had high sensitivity and NPV for CRR at 18 months. This cutoff might be used to prospectively identify patients who are unlikely to achieve complete response within 18 months on the initial therapy for LN. The impact of these findings on guiding treatment decisions outside the setting of randomized clinical trials requires further investigation.
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SAT0222 BIIB059, A MONOCLONAL ANTIBODY TARGETING BDCA2, SHOWS EVIDENCE OF BIOLOGICAL ACTIVITY AND EARLY CLINICAL PROOF OF CONCEPT IN SUBJECTS WITH ACTIVE CUTANEOUS LE

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Background: Type I interferons (IFN-I) are central to the pathogenesis of systemic lupus erythematosus (SLE). BDCA2 is a plasmacytoid dendritic cell (pDC)-specific receptor that, upon engagement, inhibits the production of IFN-I and other inflammatory mediators. Targeting BDCA2, therefore, represents an attractive therapeutic strategy for inhibiting pDC-driven inflammation that is such a key feature of SLE pathogenesis. BIIB059, an investigational anti-BDCA2 humanized monoclonal antibody, has been shown to engage BDCA2, and this interaction leads to BDCA2 internalization and the consequent in vitro inhibition of TLR-induced IFN-I production by pDCs (Pellerin 2015).
Objectives: This first-in-patient study aimed to assess safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects and clinical activity of BIIB059 in adult SLE patients with active cutaneous lupus (CLE) following administration of a single BIIB059 dose.
Methods: A Phase 1b randomized, double-blinded, placebo controlled, multicenter clinical trial was conducted in 12 adult SLE subjects (meeting 1997 ACR criteria) with active cutaneous manifestations (including acute, sub-acute and/or chronic cutaneous forms of cutaneous lupus erythematosus (CLE)). Subjects received a single IV administration of either BIIB059 20mg/kg (n=8) or placebo (n=4). A panel of IFN-responsive genes (IRG) was assessed from whole blood by qPCR at baseline and several post-dose time points. Skin biopsies from active lesions were obtained and evaluated at baseline and week 4 for IFN-regulated proteins, including MxA and IFITM3 using quantitative immunohistochemistry. CLE disease activity was assessed using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), and safety data, including adverse events (AEs) and laboratory tests, were also collected.
Results: Most SLE subjects had high IRG signatures in the blood. Skin biopsies demonstrated features of inflammation consistent with active CLE, including elevated expression of MxA and other IFN-regulated proteins. A single dose of BIIB059 decreased the expression of IRG in blood and MxA and IFITM3 proteins in the skin in most patients. CD45+ cells were reduced in skin biopsies of BIIB059-treated patients. The reduction in inflammatory cells as well as MxA and IFITM3 expression at week 4 correlated with improvement in CLASI activity score at multiple timepoints post-dose. BIIB059 was generally well tolerated with no discontinuations due to AEs. The incidence of AEs was similar between BIIB059- and placebo-treated SLE subjects, and most AEs were mild or moderate in severity.
Conclusions: A single dose of BIIB059 resulted in inhibition of the IRG in peripheral blood and MxA and IFITM3 expression in lesional skin of SLE subjects, consistent with BIIB059's proposed mechanism of action. The clinical and biomarker data together confirm the role of human pDCs in the pathogenesis of SLE, and support further development of BIB059 in SLE.
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SAT0223 INDIRECT COMPARATIVE CLINICAL EFFECTIVENESS OF INTRAVENOUS AND SUBCUTANEOUS FORMULATIONS OF BELIMUMAB FOR THE TREATMENT OF ADULT PATIENTS WITH ACTIVE, AUTOANTIBODY-POSITIVE SYSTEMIC LUPUS ERYTHEMATOSUS WITH HIGH DISEASE ACTIVITY

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Background: The efficacy of belimumab (BEL) vs placebo (PBO), in adult

Abstract SAT0223 – Table 1

	BLISS-52 IV (10 mg/kg)		BLISS-76 IV (10 mg/kg)		North East Asia IV (10 mg/kg)		BEL112341 SC (200 mg)	
	BEL	PBO	BEL	PBO	BEL	PBO	BEL	PBO
Baseline characteristics				*HDA subgroup/original RCT (n/N)*				
	134/273	131/275	171/290	156/287	292/451	135/226	248/556	108/280
SELENA-SLEDAI score, mean (SD)	10.3 (3.4)	11.4 (4.1)	10.8 (4.0)	10.8 (3.7)	10.4 (3.8)	11.3 (4.0)	11.5 (3.3)	11.7 (3.1)
SRI response at 52 weeks, %	45.5	28.2	56.1	34.6	54.0	34.1	64.6	47.2
Outcome at 52 weeks				*Odds ratio SC/IV (95% credibility interval)*				
HDA criteria		1				2		
SRI response		0.90 (0.53, 1.52)				0.88 (0.58, 1.33)		
4-point reduction in SELENA-SLEDAI		0.99 (0.58, 1.68)				0.95 (0.63, 1.43)		
Rate of severe flares		0.69 (0.37, 1.28)				0.89 (0.53, 1.50)		

patients with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard SLE therapy has been demonstrated. To date, no direct comparison of intravenous (IV) BEL vs subcutaneous (SC) BEL has been performed, hence the importance of an indirect treatment comparison (ITC).

Objectives: To indirectly compare the clinical effectiveness of BEL IV and SC formulations in patients with SLE high disease activity (HDA) via an ITC.

Methods: Three BEL IV Phase lll randomised controlled trials (RCTs; HDA/BLISS-52, 327/577; HDA/BLISS-76, 265/548; HDA/North East Asia study [BEL113750], 427/677) and one BEL SC RCT (HDA/BEL112341; 356/836) were compared via a Bayesian ITC (BEL207255). We evaluated the relative efficacy of the formulations in patients meeting three measures of HDA at baseline (1. BLISS-52 and BLISS-76, C3 <0.9 g/L or C4 <0.16 g/L; BEL112341 and BEL113750, C3 <0.9 g/L or C4 <0.10 g/L; and 2. anti-dsDNA positive [≥30 IU/mL] or 3. Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index [SELENA-SLEDAI] scores ≥10). Analyses were conducted in patients meeting Criteria 1: low C3/C4 and high anti-dsDNA; and Criteria 2: low C3/C4 and high anti-dsDNA or SELENA-SLEDAI ≥10 or low C3/C4. The primary endpoint was SLE Responder Index (SRI) response (≥4-point reduction in SELENA-SLEDAI, no worsening in Physician's Global Assessment, no new 1A/2B British Isles Lupus Assessment Group domain scores) at Week 52. Secondary endpoints included ≥4-point reduction in SELENA-SLEDAI and SLE Flare Index rate. Safety endpoints were not assessed.

Results: Baseline characteristics were relatively similar between RCTs and a fixed effects model binomial distribution with logit link was used for all efficacy endpoints (Table). In this indirect comparison, no differences were identified between BEL IV and BEL SC for the efficacy endpoints.

Conclusions: In this indirect comparison, BEL IV and BEL SC were similar for SRI response, ≥4-point reduction in SELENA-SLEDAI, or rate of severe flare at Week 52 in patients with SLE. Outcomes were consistent irrespective of the criteria applied.

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SAT0224 THE ROLE OF INTENSIVE IMMUNOSUPPRESSIVE THERAPY IN THE MANAGEMENT OF SLE-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION: A SINGLE-CENTER COHORT STUDY

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Background: Autoimmune and inflammatory mechanisms could play a significant role in the pathogenesis of pulmonary arterial hypertension (PAH), especially in patients with systemic lupus erythematosus (SLE). The effect of immunosuppressive therapy in the treatment of SLE-associated PAH (SLE-PAH) has not been fully investigated in a large cohort previously.

Objectives: We aimed to review the clinical outcomes in patients with SLE-PAH cohort treated with intensive immunosuppressive therapy with or without PAH-targeted therapy.

Methods: In this single-center cohort study, 126 patients with SLE-PAH were consecutively enrolled between May 2006 through December 2015. All patients were performed right heart catheriazation to confirm the diagnosis of PAH, and all received intensive immunosuppressive therapy including combination of high-dose glucocorticosteroids and immunosuppressants, such as cyclophosphamide, mycophenolate and calcineurin inhibitors. Baseline demographics, clinical features, laboratory findings, hemodynamic measurements and treatment were analyzed. Kaplan-Meier curves and Cox proportional hazards regression analysis were used to evaluate the role of intensive immunosuppressive therapy.

Results: Of the 126 SLE-PAH patients, eighty-two (65.1%) patients received PAH-targeted therapy at baseline. Demographic and clinical characteristics were shown in Table 1. Survival analysis indicated that responders had a better survival than nonresponders in both with and without PAH-targeted therapy groupPatients with a shorter SLE disease duration (p=0.009) and better baseline pulmonary hemodynamics (mean pulmonary arterial pressure, pulmonary vascular resistance and Cardiac index, p<0.001) were more likely to benefit from immunosuppressive therapy (Table 1).

Table1.Comparison of clinical characteristics in responders and nonresponders to immunosuppressive therapy

	SLE-PAH without target therapy			SLE-PAH with target therapy		
	Responder N=29	Nonresponder N=15	*p-value*	Responder N=44	Nonresponder N=38	*p-value*
Female, n, (%)	29(100)	15(100)	*1.000*	43(100)	37(97.4)	*1.000*
Age, years	33.8±9.2	37.0±10.0	*0.293*	32.1±7.2	35.3±8.3	*0.066*
SLE Disease duration, months	3.5(0,23.7)	6.4(1.0,33.1)	*0.090*	4.8(0,18.9)	6.3(0.7,23.1)	*0.427*
RP,n(%)	19(65.5)	9(60.0)	*0.718*	24(54.5)	24(63.2)	*0.430*
Anti-u1RNP, n (%)	21(72.4)	10(66.7)	*0.676*	25(61.0)	19(50.0)	*0.326*
SLEDAI-2000	7.0±6.2	5.1±4.5	*0.296*	3.0±2.9	3.5±2.6	*0.420*
WHO functional classification						
I-II, n(%)	17(58.6)	5(33.3)	*0.013*	21(47.7)	18(47.6)	*0.292*
III-IV, n(%)	12(41.4)	10(66.7)		23(52.3)	20(52.6)	
6MWD, meter	465.3±77.4	424.0±97.9	*0.180*	417.8±99.4	398.2±92.9	*0.409*
Mean RAP, mmHg	4.2±3.0	2.8±2.8	*0.201*	3.9±4.3	4.3±4.0	*0.706*
Mean PAP, mmHg	37.9±8.2	45.7±7.9	*0.005*	45.1±10.3	53.2±11.0	*0.001*
CI, $l.min^{-1}.m^{-2}$	3.2±0.7	2.5±0.6	*0.003*	2.8±0.6	2.4±0.8	*0.018*
PVR, WU	6.6±2.4	10.5±3.0	*0.001*	9.2±3.6	12.7±4.5	*0.000*

Conclusions: Intensive immunosuppressive therapy markedly improved the long-term outcomes of SLE patients with PAH, especially in the early stage of PAH.

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SAT0225 CEREBLON MODULATOR CC-220 DECREASES NAÏVE AND MEMORY B CELLS AND PLASMACYTOID DENDRITIC CELLS IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS: EXPOSURE-RESPONSE RESULTS FROM A PHASE 2A PROOF OF CONCEPT STUDY

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Background: CC-220 is a cereblon E3 ligase modulatory compound currently in development for the treatment of Systemic Lupus Erythematosus as well as other autoimmune conditions and multiple myeloma. As a high affinity ligand for cereblon, CC-220 administration results in significant reductions in ikaros (IKZF1) and aiolos (IKZF3), transcription factors which are genetically linked to SLE risk, and are overexpressed in the peripheral blood of SLE patients compared to healthy controls.

Objectives: To describe the pharmacokinetics (PK), pharmacodynamics (PD), and the PK-PD relationship of CC-220 in subjects with SLE.

Methods: CC-220-SLE-001 is a randomized, double-blinded, placebo-controlled,