SATURDAY, 17 JUNE 2017

SLE, Sjögren's and APS - treatment

SAT0219 EFFICACY AND SAFETY OF ATACICEPT IN PATIENTS WITH HIGH DISEASE ACTIVITY IN A 24-WEEK, RANDOMIZED, PLACEBO-CONTROLLED, PHASE IIB STUDY (ADDRESS II)

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Background: Atacicept targets B-cell stimulating factors BLyS and APRIL, and has shown evidence of clinical response in SLE.
Objectives: Exploration of atacicept efficacy and safety in a pre-defined subpopulation of SLE patients with high disease activity (HDA, SLEDAI-2K $\geq$10 at Screening) in the phase IIb ADDRESS II study (NCT01972568).
Methods: Autoantibody positive patients on standard of care therapy were randomized 1:1:1 to double-blind weekly SC injections of atacicept 75 or 150 mg or placebo (PBO) for 24 weeks. Analyses of the HDA subpopulation are now reported.
Results: 52% of the ITT population had HDA (n=158: 52 PBO; 55 atacicept 75 mg; 51 atacicept 150 mg). 92% were female, 67% were white, and baseline characteristics were balanced between groups. At week 24 (Table 1; Figure 1), the proportion of SLE Responder Index (SRI)-4 ($p<0.05$) and SRI-6 ($p<0.005$) responses was greater with atacicept 150 mg vs PBO. BICLA response rate was higher with both doses ($p<0.05$). More patients achieved SLEDAI-2K $\leq$2 with atacicept 150 mg vs PBO ($p<0.01$). Time to severe and moderate-severe flare was significantly reduced at both atacicept doses vs PBO ($p<0.05$). Patients in the quartile with the largest decline in serum IgG had the highest SRI-6 response rates (Table 2). Treatment-emergent adverse event (TEAE) rates were similar between groups (PBO 71.2%; 75 mg 78.2%; 150 mg 74.5%). Serious/severe infections were not increased with atacicept 150 mg (PBO 9.6%; 75 mg 10.9%; 150 mg 0%). There were no patient deaths.
Conclusions: In SLE patients with HDA, Atacicept 150 mg demonstrated significant clinical responses and an acceptable safety profile.
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Table 1. Disease activity endpoints at week 24

	Placebo n=52	Atacicept 75 mg n=55	Atacicept 150 mg n=51
SRI-4 response, n (%)	22 (42.3)	32 (58.2)	32 (62.7)*
SRI-6 response, n (%)	15 (28.8)	23 (41.8)	28 (54.9)†
BICLA response¶, n (%)	14 (29.2)	26 (50.0)*	25 (49.0)*
SLEDAI-2K $\leq$2¶, n (%)	7 (13.7)	11 (20.0)	20 (39.2)†
Clinical SLEDAI-2K $\leq$2‡, n (%)	15 (28.9)	24 (43.6)	25 (49.0)*
Severe flare by SFI, n (%)	13 (25.0)	5 (9.1)	3 (5.9)
Time to severe flare by SFI, HR (95% CI)		0.33 (0.12, 0.94)*	0.19 (0.05, 0.68)†
Severe flare by BILAG A, n (%)	12 (23.1)	1 (1.8)	4 (7.8)
Time to severe flare by BILAG A, HR (95% CI)		0.08 (0.01, 0.59)†	0.32 (0.10, 0.99)*
Moderate/severe flare by BILAG A/2B, n (%)	13 (25.0)	5 (9.1)	5 (9.8)
Time to moderate/severe flare by BILAG A/2B, HR (95% CI)		0.33 (0.12, 0.95)*	0.34 (0.12, 0.95)*
Any flare by BILAG A/B, n (%)	31 (59.6)	23 (41.8)	17 (33.3)
Time to any flare by BILAG A/B, HR (95% CI)		0.67 (0.38, 1.17)	0.47 (0.26, 0.86)*

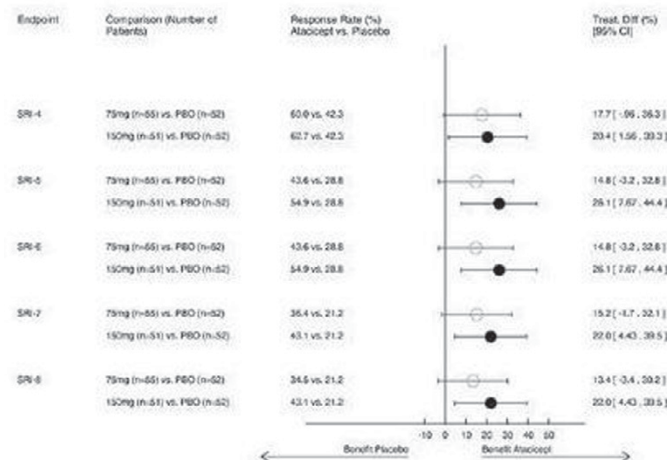
*$p<0.05$; †$p<0.01$; ‡excluding anti-dsDNA and complement parameters; HR, hazard ratio, SRI, SLE responder index; ¶patients with baseline data used for % calculation.

Table 2. Serum IgG reduction by quartile and SRI-6 response at week 24

IgG reduction (by quartile), g/L	Q1 (0–2.97) (n=21)	Q2 (2.98–4.30) (n=26)	Q3 (4.31–5.56) (n=26)	Q4 (5.57–14.73) (n=33)
SRI-6 response rate (%)	38.1	30.8	53.8	63.6
Δ vs Q1 (%)	[Referent]	-7.3	15.7	25.5

SRI, SLE Responder Index.

Figure 1. Forest Plot for SRI Response at Week 24 with Screening Visit as baseline HDA Population



SAT0220 EFFECTS OF TYPE I INTERFERON INHIBITION ON BLOOD LEUKOCYTE SUBSETS IN PATIENTS TREATED IN A PHASE IIB CLINICAL STUDY OF ANIFROLUMAB IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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Background: A Phase IIb randomized controlled study (NCT01753193) was conducted with anifrolumab, a fully human, anti-interferon (IFN)–α receptor (IFNAR) specific antibody in adults with moderate to severe SLE. Anifrolumab binds to subunit 1 of the IFNAR and inhibits the activity of all type I IFNs. A complete blood count analysis demonstrated that anifrolumab reversed leukopenia. However, the types of peripheral immune cells affected following treatment have not been reported.
Objectives: To better understand how changes in the immune cell repertoire may be associated with SLE severity, type I IFN test status (high vs. low), and treatment with anifrolumab, we performed flow cytometry to assess peripheral blood cell types: dendritic cells (myeloid and plasmacytoid), B cells (naïve, memory, and plasma cells), neutrophils, and T cells (CD4, CD8, naïve, memory, central memory, and effector).
Methods: Patients were randomized 1:1:1 to anifrolumab 300 mg, or 1,000 mg, or placebo (PBO) every 4 weeks for 48 weeks. Peripheral blood was collected from a subset of patients (91 total) on Days 1 (prior to first dose), 85, 141, 169, 253, 337, and 365. Patients were approximately evenly distributed between treatment arms. Baseline absolute immune cell numbers were compared over treatment course in the context of SLE Disease Activity Index (SLEDAI)–2K scores, type I IFN test, and therapy response. Statistics were calculated using the Student's *t*-test; p-values $\leq$0.05 were considered statistically significant.
Results: At baseline, several blood cell types were lower for patients with SLEDAI $\geq$10, including naïve B cells, and memory T and B cells. In IFN-high patients, neutrophils, memory T cells, and plasmacytoid dendritic cells (pDCs) were significantly decreased. Anifrolumab led to significant increases in absolute numbers of T-cell subsets in the blood of IFN-high patients. In contrast, no significant changes were observed for IFN-low patients. Observed increases were within normal reference ranges. The alterations did not appear to be secondary to tapering of oral corticosteroids, as these cell types were not significantly different in PBO groups, regardless of tapering. Patients with $\geq$6-point SLEDAI reductions following anifrolumab demonstrated significant increases in total CD4 and CD8 T cells, and nonsignificant decreases in memory B cells. Significant increases in pDCs were also evident. Anifrolumab did not cause significant differences in other cell types measured.
Conclusions: Memory T cell numbers, among other cell types, were significantly reduced in patients with SLEDAI $\geq$10 and those classified as IFN high at baseline. This suggests that, for patients with more severe disease, type I IFN may be involved in cell migration into the peripheral tissues from the blood. Consistent with this, we found that neutralization of type I IFN with anifrolumab promoted immigration and/or prevented emigration of potentially pathologic immune cells between the tissues and the blood. These data suggest that some effects observed following anifrolumab treatment might be a result of altering the migration patterns of T and other immune cells, which may partially explain its biological activity.
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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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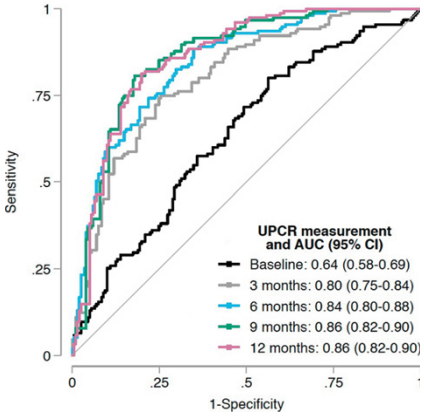
Background: Early identification of patients with lupus nephritis (LN) likely to achieve complete renal response (CRR) may expedite the evaluation of new therapies and guide clinical care. Prior analyses have shown that early improvement in proteinuria is associated with subsequent renal response.[1,2] 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.
References:
[1] Tamirou Lupus Sci & Med 2015.
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[4] Rovin B Arthritis Rheumatol 2012.
[5] Mysler E Arthritis Rheumatol 2013.
[1] Trial registry numbers: NCT00282347 (LUNAR) and NCT00626197 (BELONG).
Disclosure of Interest: M. Cascino Employee of: Roche/Genentech, T. Schindler Employee of: Roche/Genentech, L. Gomez Mendez Grant/research support from: Roche/Genentech, P. Brunetta Employee of: Roche/Genentech, L. Dragone Employee of: Roche/Genentech, M. Dall'Era: None declared, J. Garg Employee of: Roche/Genentech
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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.
Disclosure of Interest: R. Furie Consultant for: Biogen, V. Werth Grant/research support from: Biogen, Consultant for: Biogen, J. Merola Grant/research support from: Biogen, Consultant for: Biogen, AbbVie, Amgen, Eli Lilly, Novartis, Pfizer, Janssen, Mallinckrodt, Momenta, Speakers bureau: AbbVie, Eli Lilly, T. Reynolds Shareholder of: Biogen, Employee of: Biogen, L. Stevenson Shareholder of: Biogen, Employee of: Biogen, W. Wang Shareholder of: Biogen, Employee of: Biogen, K. Smirnakis Shareholder of: Biogen, Employee of: Biogen, C. Barbey Shareholder of: Biogen, Employee of: Biogen, C. Musselli Shareholder of: Biogen, Employee of: Biogen, B. Werneburg Shareholder of: Biogen, Employee of: Biogen, D. Rabah Shareholder of: Biogen, Employee of: Biogen, N. Franchimont Shareholder of: Biogen, Employee of: Biogen
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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