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)*

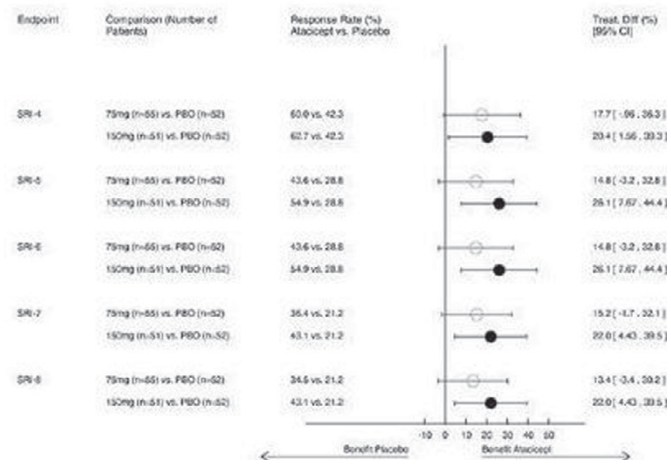
*$p<0.05$; †$p<0.01$; ‡excluding anti-dsDNA and complement parameters; HR, hazard ratio, SRI, SLE responder index; ¶patients with baseline data used for % calculation.

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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