Evaluation of American College of Rheumatology Provisional Composite Response Index in Systemic Sclerosis in a Phase II Trial of Abatacept vs. Placebo

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Abstract #1716

BACKGROUND

- Treatment with CTLA4Ig, abatacept (ABA), in early diffuse cutaneous systemic sclerosis (dcSSc; the Phase 2 ASSET trial) showed evidence of improvements in modified Rodnan skin score (mRSS) and secondary outcome measures at month 12 (2018 ACR abstract # 900).
- The CRISS index, a composite outcome measure for trials in SSc[1], is a 2-step process that assigns a probability of improvement for each subject ranging from 0.0 [no improvement] to 1.0 [marked improvement].
- Step 1 assesses clinically meaningful decline in cardio-pulmonary-renal involvement with a probability of 0.0.
- For remaining subjects, probability of improvement is based on 5 variables: changes from baseline to month 12 in FVC%, mRSS, patient (PTGA) and physician global assessments (MDGA), and HAQ-DI.
- We assessed the performance of CRISS, a secondary outcome measure, in ASSET at month12.

METHODS

- ASSET was an investigator-initiated, multicenter double-blind, randomized placebo-controlled trial.
- Eligible subjects were randomized in a 1:1 ratio to either 12 months 125 mg subcutanoues ABA or matching placebo, stratified by duration of dcSSc (≤18 vs >18 to ≤36 months).
- Investigators reported SSc end organ involvement (Step 1 for CRISS) prospectively.
- These and all AEs and SAEs were reviewed for cardio-pulmonary and renal involvement by the study PI.
- Step 2 calculated the CRISS index as previously defined[1].

METHODS

- Treatment differences, adjusted for duration of dcSSc, in the CRISS score were assessed by the non-parametric van Elteren test and by ANCOVA for individual CRISS components.
- We calculated Spearman's correlation coefficients to assess the relationship between the CRISS score and its individual components.
- Multiple imputation was used for analysis, creating 25 complete datasets with estimates, standard errors and p-values pooled over each imputed dataset.

RESULTS

- 88 subjects (44 ABA, 44 PBO) were randomized; 63 (72%) had complete data for all relevant outcomes at month 12.
- 5 PBO and 5 ABA subjects met the pre-defined definition of worsening cardio-pulmonary-renal involvement (Table 1) and were given a score of 0.0.

Table 1: Number of patients meeting the Step 1 endpoint

CRISS	ABA	PBO*
New PAH	1	1
Worsening ILD	1	3
New LVEF≤45%	0	1
New Renal Crisis	3	1

*Note: one patient experienced 2 events (PAH and ILD)

- There is evidence of improved CRISS scores on ABA compared to the PBO at month 12 and the difference was statistically significant (p=0.01; Table 2).
- Similar trends were seen in those with early disease (0-18 months) and late disease (>18 to 36 months).

RESULTS

Table 2: Comparison of ABA and PBO using CRISS index (0.0-1.0) at 12 mths

Overall	ABA N=44	PBO N=44	P-value
CRISS median (IQR)	0.68 (0.99)	0.01 (0.81)	0.03*
CRISS ≥ 0.60	62.8%	37.2%	0.01**
0-18 months duration of dcSSc	ABA N=26	PBO N=27	P-value^
CRISS median (IQR)	0.70 (0.99)	0.02 (0.78)	0.24
>18-36 months duration of dcSSc	ABA N=18	PBO N=17	P-value^
CRISS median (IQR)	0.60 (0.99)	0.00 (0.93)	0.05

* van Elteren test, adjusting for duration of dcSSc
**Cochran-Mantel-Haenszel test, adjusting for duration of dcSSc
^p-value for treatment comparisons based on Wilcoxon test

Table 3: Comparison of ABA and PBO using individual components at 12 months for overall group

Outcome	ABA N=44	PBO N=44	Treatment Diff (ABA-PBO)	
	LS mean (SE)	LS mean (SE)	LS mean (SE)	P-value^
ΔmRSS (0-51)	-6.7 (1.30)	-3.7 (1.19)	-2.9 (1.70)	0.09
ΔFVC% predicted	-1.4 (1.48)	-3.3 (1.24)	1.9 (1.93)	0.33
ΔPTGA (0-10)	-0.48 (0.392)	-0.32 (0.391)	-0.16 (0.550)	0.77
ΔMDGA (0-10)	-1.31 (0.273)	-0.15 (0.279)	-1.20 (0.394)	0.003
ΔHAQ-DI (0-3)	-0.11 (0.082)	0.11 (0.079)	-0.21 (0.109)	0.06

^p-value for treatment comparisons based on ANCOVA model with treatment, duration of SSc and baseline value as covariates
Negative score denotes improvement, except for FVC% where negative score denotes worsening
LS mean = least squares mean; SE=standard error

- For individual variables, MDGA was statistically significant (p=0.003) and HAQ-DI had weaker evidence of effect (p=0.06), both favoring ABA (Table 3).
- Most variables, except HAQ-DI and PTGA, had statistically significant correlations with the CRISS (Table 4).
- For 0- 18 month disease duration, the correlations were significant for ΔmRSS and ΔMDGA and for >18-36 months, it was driven by ΔmRSS, ΔMDGA, and ΔFVC (data not shown)

Table 4 : Spearman Correlations between CRISS and individual components at 12 months for overall group, N=88

Outcome	Correlation
ΔmRSS (0-51)	-0.75*
ΔFVC% predicted	0.36*
ΔPTGA (0-10)	-0.17
ΔMDGA (0-10)	-0.47*
ΔHAQ-DI (0-3)	-0.19

*p< 0.01

CONCLUSIONS

- The current data suggest that CRISS is more sensitive to clinically meaningful treatment changes than the mRSS endpoint.
- We provide further validation of CRISS as an independent primary endpoint for early diffuse scleroderma clinical trials.

REFERENCES

1. Khanna D. Arthritis Rheumatol. 2016

DISCLOSURES

- **D. Khanna Grant/research support from:** NIH/NIAMS and NIH/NIAID, Bayer, BMS, Pfizer
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