Patient-level evaluation of Components of the ACR Combined Response Index in Systemic Sclerosis (CRISS) using Patient-Reported Anchor

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INTRODUCTION

- Treatment benefit is demonstrated by evidence that interventions have positive impacts on how patients feel, function, and/or survive (FDA Regulation 21CFR314.510).
- The ACR CRISS is a composite endpoint for trials in diffuse systemic sclerosis (dcSSc) with outcome assessments that are direct measures of patient symptoms/function/survival.
- Understanding the relationship and magnitude of effects on these indirect assessments would provide confidence that each component of CRISS would reliably predict an effect on direct measures of patient benefit.

OBJECTIVE

To provide data to support evaluation of CRISS using patient-reported outcomes (PRO's) anchors, i.e. HAQ-DI and PGA.

METHODS

- We evaluated 2 cohorts: an early diffuse cutaneous SSc (dcSSc) cohort used for development of ACR CRISS [CRISS cohort (1)] and a phase 2 trial of tocilizumab vs. placebo in dcSSc [faSScinate trial cohort (2)].
- We assessed the effect size (ES) at the patient-level for non-PRO variables (mRSS, MDGA, and FVC%).
- We defined "responders" as subjects who met minimal clinically important differences (MCID) estimates for HAQ-DI (improvement of ≥ 0.22) and PGA (improvement of ≥ 1.0, range 0-10). We also explored MCID estimates of PGA improvement ≥ 2.0.
- We interpreted the ES using the Cohen's criteria [< 0.20= negligible, 0.20-0.49 = small, 0.50-0.79 = medium, >0.80 = large] (3).
- We assessed whether ES in subjects classified as responders (HAQ-DI and PGA) in the faSScinate trial was associated with larger improvements in the ACR CRISS scores at week 24 and 48.

RESULTS

Table 1: Baseline demographics in CRISS and faSScinate cohorts

	CRISS cohort N=150	faSScinate trial cohort	
		Placebo group N=44	TCZ group N=43
Age in years*	50 (11.7)	44 (12.9)	51 (11.7)
Women N (%)	150 (75%)	35 (80%)	32 (74%)
Disease duration in months	19.2 (16.8)	19.5 (17.0)	17.6 (13.9)
MRSS	20.6 (10.1)	26.0 (5.9)	26.0 (7.2)
FVC %	82.3 (18.5)	82.0 (13.0)	80.0 (14.0)
PGA	3.9 (2.7)	6.2 (2.1)	5.9 (1.8)
MDGA	4.3 (2.2)	6.1 (1.5)	6.4 (1.5)
HAQ-DI	1.0 (0.8)	1.0 (0.7)	1.0 (0.6)
DLCO%	65.0 (20.9)	74.0 (21.0)	73.0 (19.0)
TFR	40 (29%)	22 (50%)	20 (47%)

*All values are mean (SD) unless stated otherwise
TCZ = tocilizumab, MRSS = modified Rodnan Skin Score, FVC % = percent predicted forced vital capacity, PGA = patient global assessment, MDGA = physician global assessment, HAQ-DI = health assessment questionnaire disability index, DLCO % = percent predicted diffusion capacity for carbon monoxide, TFR = tendon friction rubs

Table 2: Change in the ACR-CRISS variables in responders and non-responders based on HAQ-DI and PGA MCID estimates

	Patients with HAQ-DI ≥ 0.22 (MCID) Responders	Patients with HAQ-DI <0.22 Non-responders	P value	Patients with PGA ≥ 1 (MCID)	Patients with PGA<1	P value	Patients with PGA ≥ 2 (MCID)	Patients with PGA<2	P value
CRISS cohort									
MRSS, ES	- 0.70, N= 27	- 0.30, N= 84	**0.06**	- 0.65, N= 37	- 0.25, N=74	**0.03**	-0.70, N= 24	-0.29, N= 87	**0.03**
FVC%, ES	0.20, N= 24	- 0.07, N= 87	**0.002**	0.11, N= 32	- 0.07, N=79	**0.04**	0.18, N= 21	-0.07, N= 90	**0.01**
PGA, ES	- 0.29, N= 28	0.03, N= 69	0.13	NA	NA		NA	NA	
MDGA, ES	- 0.43, N= 23	- 0.06, N= 72	0.30	- 0.31, N=31	-0.06, N=64	0.40	-0.31, N= 19	-0.09, N= 76	0.52
HAQ-DI, ES	NA	NA		- 0.14, N=37	0.10, N=62	0.16	-0.36, N= 24	0.13, N=75	**0.03**
faSScinate trial cohort									
CRISS Score at 24 week, median	0.381, N=18	0.002, N=49	**0.04**	0.229, N=21	0.018, N=46	**0.02**	0.152, N=12	0.038, N=55	0.27
CRISS Score at 48 week, median	0.947, N=15	0.011, N=43	**<0.001**	0.705, N=22	0.018, N=36	**0.01**	0.863, N=15	0.021, N=43	**0.01**

Table 3: Correlation matrix (CRISS variables)

	MRSS	FVC%	PGA	MDGA	HAQ-DI
MRSS	1.00	-0.31	0.14	0.24	0.17
FVC %	-0.31	1.00	-0.23	-0.20	-0.22
PGA	0.14	-0.23	1.00	0.23	0.15
MDGA	0.24	-0.20	0.23	1.00	0.21
HAQ-DI	0.17	-0.22	0.15	0.21	1.00

MRSS = modified Rodnan Skin Score, FVC % = percent predicted forced vital capacity, PGA = patient global assessment, MDGA = physician global assessment, HAQ-DI = health assessment questionnaire disability index

- In the CRISS cohort – (a) ES were generally of greater magnitude for responders vs. non-responders (Table 2), except for HAQ-DI and FVC% when using PGA as an anchor, (b) ES for MDGA was non-significant for responders vs. non-responders, despite large magnitude likely due to the small sample size.
- In the faSScinate trial cohort, statistically significant improvements in the median ACR CRISS scores were seen in those who attained MCID vs. patients who did not.

CONCLUSION

- In a dcSSc cohort, patients who achieved MCID in HAQ-DI and PGA were associated with larger magnitude of improvement in ACR CRISS non-PRO variables.
- HAQ-DI and PGA are part of the ACR CRISS score. This is a limitation of this analysis.
- Ongoing trials should confirm the relationships between non-PRO variables (mRSS, MDGA, and FVC%) vs. PRO anchors.

REFERENCES

1. Khanna, Dinesh, et al. Arthritis & Rheumatology 68.2 (2016): 299-311.
2. Khanna, Dinesh, et al. The Lancet 387.10038 (2016): 2630-2640.
3. Cohen, Jacob. "A power primer." Psychological bulletin 112.1 (1992): 155.

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