Patient and Physician Opinions of Clinical Benefit at 3 Months in a Clinical Trial Correlate with Patient-Reported Outcomes (PROs)

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Abstract # 159

Abstract

Introduction: A SSc patient's and treating physician's opinion of clinical benefit early in treatment are each likely important in maintaining adherence and persistence on therapy thereafter in the real-world setting. Disease-specific and non-disease-specific PROs are used to assess how people with SSc feel and function. The hypothesis of this evaluation was that both the patient's and physician's opinion of clinical benefit early in treatment (3 months) in a lenabasum phase 2 study would correlate with change in PROs.

Methods: Spearman correlations were performed between a patient's and treating physician's opinion "yes/no" on whether the patient had received clinical benefit from study product and change (Δ) in PROs and efficacy outcomes at 3 months in a double-blind placebo-controlled phase 2 study of lenabasum (JBT101-SSc-001), with 38 (88.5%) patients completing 3 months dosing. The PROs included HAQ-DI, Patient Global Assessment of Health related to SSc (PtGA), Scleroderma Skin Symptoms Patient-reported Outcome (SSPRO) questionnaire, and PROMIS-29 questionnaire domain T-scores for physical function, social role, fatigue, sleep disturbance, pain interference, anxiety, and depression domains. ACR CRISS score and Δ mRSS were obtained.

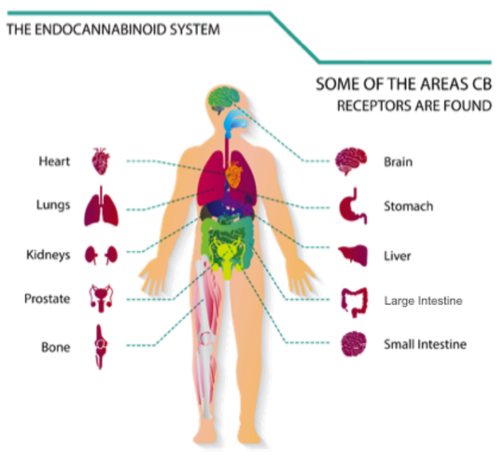
Results: Patient opinion of clinical benefit at 3 months moderately correlated in a statistically significant manner with Δ PtGA and Δ SSPRO, but not Δ HAQ-DI or Δ PROMIS-29 physical function, social role, and pain domains. Patient opinion of benefit at 3 months had low, not statistically significant, correlations with ACR CRISS score and Δ mRSS. Physician opinion of clinical benefit at 3 months correlated moderately and statistically significantly or near statistically significantly with Δ PtGA, Δ SSPRO, Δ PROMIS-29 social role and pain domains, as well as efficacy outcomes (ACR CRISS and Δ mRSS).

Conclusions: Both the patient's and physician's opinion of clinical benefit early in treatment at 3 months correlated with the patient's overall assessment of health related to SSc and change in skin symptoms. Larger and longer studies will help further elucidate what PROs reflect a SSc patient's assessment of clinical benefit from treatment.

Introduction

- Systemic sclerosis (SSc) is a potentially life-threatening autoimmune disease characterized by a triad of chronic inflammation, fibrosis, and vascular damage (Sierra-Sepúlveda et al, 2019).
- SSc results in impaired health status, a greater chronic disease burden, and increased mortality (Morrisroe et al, 2017; Zhou et al, 2019).
- The endocannabinoid system (ECS) is a naturally occurring neuro-immunomodulatory system that regulates innate immune responses and associated wound healing, pain, and energy metabolism (Buckley et al 2014; Serhan, 2014) (**Figure 1**).

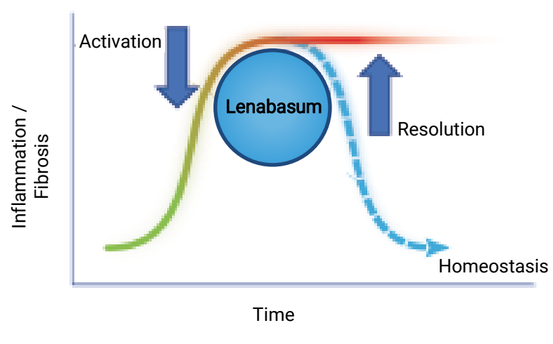
Figure 1. The Endocannabinoid System



- Ubiquitous within the body
- System of G-protein coupled receptors, lipid ligands, and enzymes that degrade ligands
- Restores homeostasis upon cellular activation
- Regulates multiple physiologic processes

- Lenabasum is an oral, selective, CB_2 agonist that activates resolution of innate immune responses (Tepper et al, 2014) (**Figure 2**).

Figure 2. Mechanism of Action of Lenabasum (Motwani et al, 2018)



- Lenabasum reduces the onset and accelerates the resolution phase of inflammation in humans.
- Lenabasum does this by acting to:
  - Inhibit neutrophil infiltration;
  - Induce a class shift from pro-inflammatory to pro-resolving lipid mediators; and
  - Enhance bacterial clearance
- These novel pharmacologic effects offer promise for lenabasum in the treatment of chronic rheumatic diseases.

- In a Phase 2 study of patients with dcSSc, lenabasum was safe and well-tolerated and was associated with improvements in the American College of Rheumatology (ACR) Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) score (Spiera et al, 2020).
- Disease-specific and non-disease-specific patient reported outcomes (PROs) are used to assess how people with SSc feel and function.
- The opinion of the patient and treating physician of the clinical benefit of lenabasum early in the treatment of dcSSc may be important factors for maintaining adherence and persistence in the real-world setting.

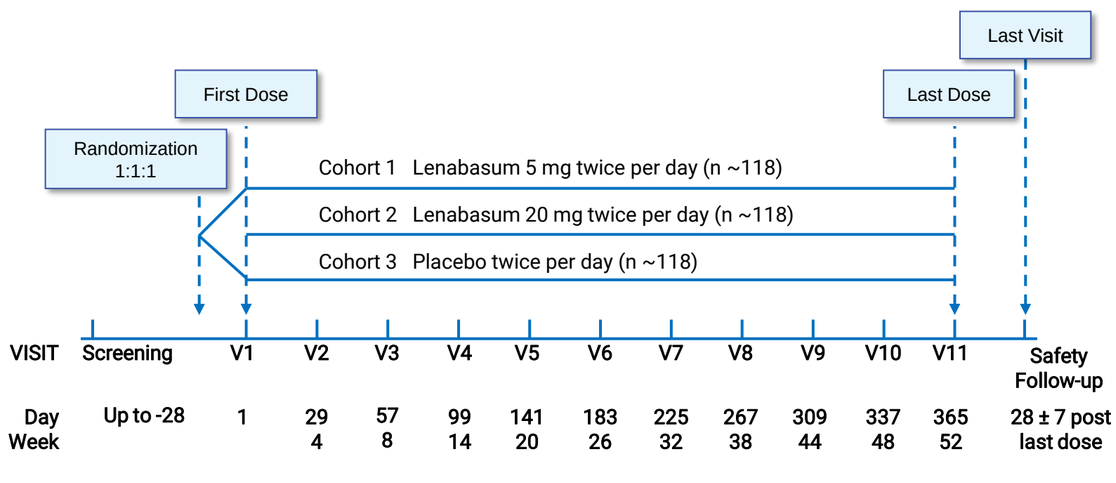
Objective

- This was a secondary analysis from a Phase 2 study of lenabasum in patients with dcSSC (Spiera et al, 2020) was to evaluate the correlation between patient and physician assessments of the clinical benefit early in treatment (3 months) with the change in PROs.

Methods

- This was a double-blind, randomized, placebo-controlled Phase 2 study conducted at nine SSc clinics (**Figure 3**).

Figure 3. Study Design



- Adults with dcSSc ≤ 6 years duration who were on stable standard-of-care treatment received lenabasum or placebo.
  - Lenabasum doses were 5 mg once daily, 20 mg once daily, or 20 mg twice daily for 4 weeks, then 20 mg twice daily for 8 weeks.
- PROs included:
  - Health Assessment Questionnaire-Disability Index (HAQ-DI)
  - Patient Global Assessment of Health related to SSc (PtGA)
  - Scleroderma Skin Symptoms Patient-reported Outcome (SSPRO) questionnaire
  - Patient-Reported Outcomes Measurement Information System-29 item (PROMIS-29) questionnaire domain T-scores for:
    - Physical function, social role, fatigue, sleep disturbance, pain interference, anxiety, and depression domains
- ACR CRISS score and Δ mRSS were measured.
- Safety and efficacy assessments were performed at weeks 4, 8, 12, and 16.

Methods (cont'd)

Study Analysis

- Spearman correlations were performed between patient and physician opinion ("yes/no") on whether the participant had received clinical benefit from lenabasum and the change (Δ) in PROs and efficacy outcomes.

Results

- Baseline characteristics of the study population were similar between groups (**Table 1**).
- 38 (88.5%) participants completed 3 months of dosing in the double-blind period.

Table 1. Baseline Characteristics of Study Population

Characteristic	Lenabasum (N = 27)	Placebo (N = 15)
Age, years*	49 ± 10.4	47 (11.1)
Female sex, n (%)	23 (85.2)	9 (60.0)
White, n (%)	22 (81.5)	12 (80.0)
mRSS*	24 ± 10.4	26 ± 11.1
Disease duration, months*	34 ± 16.6	33 ± 17.9
Patient Global Assessment*	4.9 ± 2.3	4.9 ± 2.8
Physician Global Assessment*	4.6 ± 1.8	5.2 ± 2.1
HAQ-DI*	1.5 ± 0.8	1.3 ± 0.8
Concomitant immunosuppressive medicines (%)	93%	80%

* Mean ± standard deviation

- A directionally correct correlation was observed between physician or patient clinical benefit and Δ HAQ-DI or between patient clinical benefit and Δ PROMIS-29 physical function, social role, and pain domains (**Table 2**).
- Physician opinion of clinical benefit at 3 months had a moderate, directionally correct, and statistically significant correlation or near statistically significant correlation with Δ PtGA, Δ SSPRO, Δ PROMIS-29 social role and pain domains (**Table 2**).
- Patient opinion of clinical benefit at 3 months had a moderate, directionally correct, and statistically significant correlation with Δ PtGA and Δ SSPRO (**Table 2**).

Table 2. Correlation of Physician and Patient Opinions of Clinical Benefit with Patient-Reported Outcomes (PROs) at 3 Months

Opinion of Clinical Benefit	HAQ-DI	PROMIS-29 Domains			PtGA	SSPRO
		Physical Function	Social Role	Pain Interference		
Physician	-0.03	0.19	0.34**	-0.38**	-0.34**	-0.31*
Patient	-0.03	-0.13	0.00	-0.22	-0.35**	-0.38**

*p < 0.06; **p < 0.05

- Physician opinion of clinical benefit was strongly and statistically significantly correlated with efficacy outcomes (ACR CRISS and Δ mRSS) (**Table 3**).
- Patient opinion of clinical benefit at 3 months was directionally correct with positive but not statistically significant correlations with ACR CRISS score and Δ mRSS (**Table 3**).

Table 3. Correlation of Physician and Patient Opinions of Clinical Benefit with Patient-Reported Outcomes (PROs) at 3 Months

Opinion of Clinical Benefit	ACR CRISS Score (median)	Change in mRSS from Baseline
Physician	0.74*	-0.62*
Patient	0.28	-0.22

*p < 0.0001

Summary and Conclusions

- Both physician and patient opinion of the clinical benefit of lenabasum at 3 months correlated with the overall assessment of health related to SSc and change in skin symptoms.
- Larger studies will further elucidate the value of specific PROs to reflect the clinical benefit from lenabasum.
- The ongoing RESOLVE-1 study is a 52-week, randomized, placebo-controlled study evaluating lenabasum for the treatment of patients with dcSSc.
- To confirm these initial findings, results from RESOLVE-1 will include correlations between participant and physician assessments of benefit and changes in efficacy outcomes and ACR CRISS.

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Poster presented at the 6th Systemic Sclerosis World Congress; 5-7 March, 2020; Prague, Czech Republic