Effect of Anabasum (JBT-101) on Gene Expression in Skin Biopsies from Subjects with Diffuse Cutaneous Systemic Sclerosis (dcSSc) and the Relationship of Baseline Molecular Subsets to Clinical Benefit in the Phase 2 Trial

Poster # 1707

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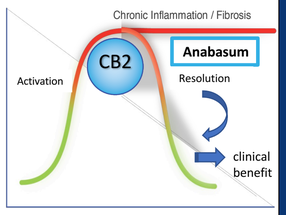
Background/Purpose

Anabasum (JBT-101) is a non-immunosuppressive synthetic CB2 agonist that resolves inflammation and fibrosis in animal models of SSc and reduces TGF-β and collagen production by dcSSc fibroblasts.

It showed evidence of clinical benefit in dcSSc in the Phase 2 trial JBT101-SSc-001 (NCT02465437). To provide additional data on the impact of anabasum on SSc, we analyzed gene expression changes in skin biopsies from trial subjects.

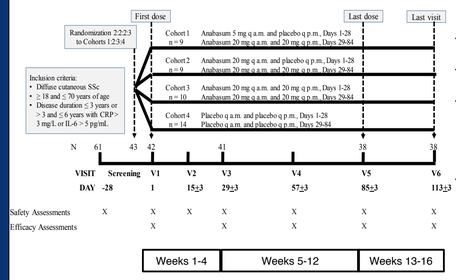
Chronic Inflammation/Fibrosis



Methods

Gene expression data at baseline and end of treatment (Day 85) were used for differential gene expression, pathway enrichment and intrinsic subset assignment, comparing paired skin biopsies from anabasum-treated (N=23) and placebo-treated (N=13) subjects. Overall response was an ACR Composite Response Index in dcSSc (CRISS) score of ≥ 0.2 and skin response was a decrease in modified Rodnan Skin Score (mRSS) ≥ 5 points.

Study Schematic of Double-Blinded Placebo-Controlled Phase 2 Trial JBT101-SSc-001



Inclusion Criteria:

- ✓ Diffuse cutaneous system sclerosis
- ✓ ≥ 18 and ≤ 70 years of age
- ✓ Disease duration ≤ 3 years or > 3 and ≤ 6 years with CRP > 3 mg/l or IL-6 > 5 pg/mL
- ✓ Concomitant medicines for systemic sclerosis, including immunosuppressive drugs, are allowed

Results

1937 genes were differentially expressed in anabasum arm (False Discovery Rate ≤ 5%) from baseline to Day 85. Genes downregulated from baseline at Day 85 were enriched in *inflammatory response, extracellular matrix (ECM) organization, collagen metabolism, response to cytokine* and *angiogenesis* (Bonferroni-corrected p ≤ 0.05). Genes upregulated from baseline at Day 85 were involved in *lipid metabolism* and related GO terms. These changes were not observed in the placebo arm (Table 1).

Table 1. Sample GO terms and their p-values in anabasum and placebo arms. P-values are for Fisher's one-tailed test followed by Bonferroni correction for multiple testing.

Sample GO terms	Anabasum arm	Placebo arm
Downregulated post-treatment:		
- *ECM organization*	1.2E-11	1
- *Inflammatory response*	7.3E-07	1
- *Collagen metabolism*	8.5E-07	1
- *Response to cytokine*	2.2E-04	1
- *Angiogenesis*	1.0E-02	1
Upregulated post-treatment:		
- *Lipid metabolism*	2.7E-13	1
- *Fatty acid metabolism*	1.3E-10	1
- *Lipid biosynthesis*	2.2E-08	1
- *Peroxisome*	1.2E-05	1

Inflammatory response and *ECM organization* pathways included many genes important in SSc (e.g. CCL2, CTGF, FN1, ICAM1, IL4R, PDGFB, TGFB1, THBS1, TIMP1 and TNC). *Inflammatory response* genes decreased in the anabasum arm (Figure 1A, p < 0.0001) but not the placebo arm (Figure 1B, p = 0.3054). Similar reduction was also observed for *ECM organization* genes (p = 0.0002 for anabasum vs. p = 0.4840 for placebo).

Most CRISS (83%) and all mRSS improvers in the placebo arm were assigned to normal-like intrinsic gene expression subset whereas in the anabasum arm most CRISS (75%) and mRSS (79%) improvers were classified as inflammatory or fibroproliferative (Figure 1C and 1D). Scleroderma Disease Severity Score (SDSS), a gene expression-based mRSS surrogate, decreased at Day 85 in anabasum-treated (Figure 1E, p = 0.0029) but not placebo-treated subjects (Figure 1F, p = 0.9576).

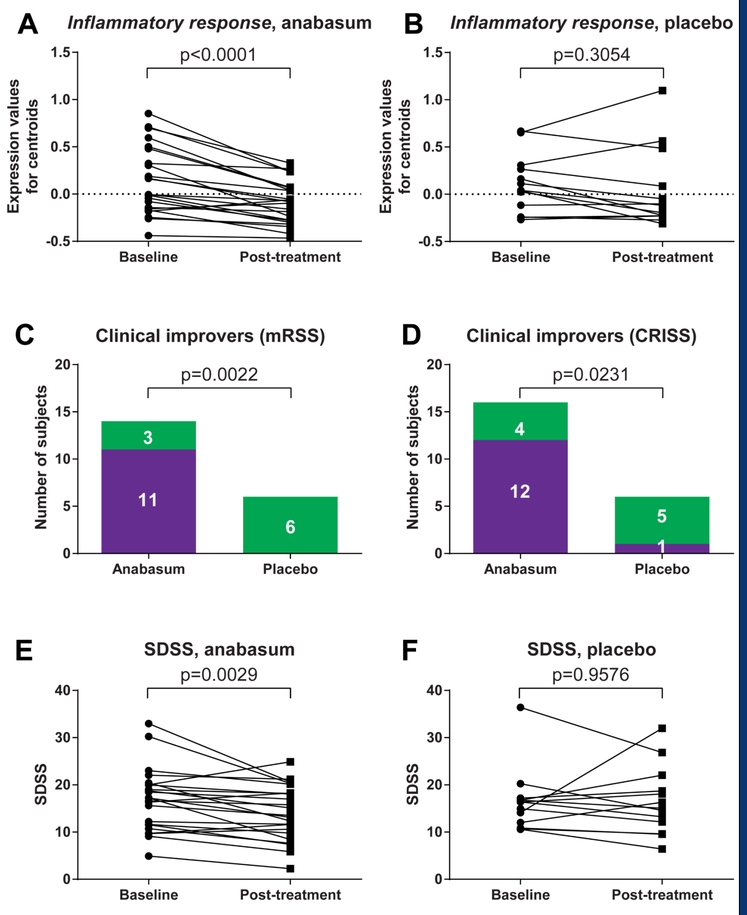


Figure 1. Effect of anabasum (JBT-101) on gene expression in dcSSc. Changes in *inflammatory response* pathway in anabasum (A) and placebo (B) arms. Clinical improvers by treatment arm and intrinsic gene expression subset as defined by mRSS (C) and CRISS (D). Changes in SDSS (quantitative surrogate of mRSS) in anabasum (E) and placebo (F) arm. For panels A/B and E/F, p-values are for paired t-test. For panels C and D, p-values are for Fisher's exact test. For panels C/D, clinical improvers classified as inflammatory or fibroproliferative are marked purple and those classified as normal-like are marked green.

Conclusion

Anabasum induced clinically relevant molecular responses by modulating inflammatory and fibrotic genes and pathways consistent with the resolution of innate immune signaling. Changes in gene expression in the skin of anabasum-treated subjects were accompanied by improvement in CRISS, mRSS and SDSS. Majority of anabasum improvers had increased baseline inflammatory or fibroproliferative gene expression in skin whereas placebo improvers nearly all had increased normal-like gene expression at baseline. This suggests that the normal-like subset identifies subjects that are more likely to improve spontaneously. This report supports further clinical testing of efficacy of anabasum in dcSSc.

Study Sponsors

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Disclosures

Disclosure: V. Martyanov, None; **Y. Nesbeth**, Celdara Medical, LLC, 3; **G. Cai**, None; **T. A. Wood**, Celdara Medical, LLC, 5; **J. Reder**, Celdara Medical, LLC, 1,Celdara Medical, LLC, 3,Celdara Medical, LLC, 4,Celdara Medical, LLC, 6; **S. Constantine**, Corbus Pharmaceuticals, Inc., 1,Corbus Pharmaceuticals, Inc., 3; **B. White**, Corbus Pharmaceuticals, 1,Corbus Pharmaceuticals, 3; **R. F. Spiera**, Roche-Genentech, 2,GSK, 2,BMS, 2,Celgene, 2,Boehringer Ingelheim, 2,Cytori, 2,Chemocentryx, 2,Corbus Pharmaceuticals, 2,Prism, 2,Roche-Genentech, 5,GSK, 5,Boehringer Ingelheim, 5; **M. L. Whitfield**, Corbus, UCB, GSK, 5,Celdara Medical, LLC, 9.

For related clinical data from the trial, please see the following posters and presentation:
Spiera et al., Poster # 725, Safety and Efficacy of Anabasum (JBT-101) in Diffuse Cutaneous Systemic Sclerosis (dcSSc) Subjects Treated in an Open-Label Extension of Trial JBT101-SSc-001; 11/5, 9 – 11am
Rob Spiera, Oral Presentation, Abstract # 2884, A Phase 2 Study of Safety and Efficacy of Anabasum (JBT-101), a Cannabinoid Receptor Type 2 Agonist, in Diffuse Cutaneous Systemic Sclerosis; 11/7, 4:30 – 6pm
Man et al., Poster # 738, Prospective Validation of the Systemic Sclerosis Skin Symptoms Patient-Reported Outcome (SSPRO) in a Phase 2 Trial of Anabasum (JBT-101) in Diffuse Cutaneous Systemic Sclerosis (dcSSc)