Anabasum (JBT-101) Enhances Resolution of Inflammation in Humans

Poster # 298

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Abstract

Background/Purpose: Certain rheumatic diseases including systemic sclerosis (SSc) are characterized by chronic activation of innate immune responses, leading to excessive fibrosis. A normal innate immune response is comprised of an onset phase characterised by generation of pro-inflammatory lipid mediators, chemokines, adhesion molecules, and tissue infiltration of inflammatory cells. This is followed by a resolution phase where the balance of lipid mediators shifts from pro-inflammatory mediators to novel Specialized Pro-resolving Lipid Mediators (SPMs), pro-inflammatory cytokines and chemokines are inhibited, pathogens and inflammatory cells are cleared from involved tissues, and active wound healing processes are completed. Persistent inflammation and progressive fibrosis can reflect an imbalance that favors the onset phase over resolution phase. Anabasum (JBT-101) is a cannabinoid receptor type 2 agonist that showed evidence of clinical benefit on Phase 2 testing in systemic sclerosis. Anabasum activates resolution of skin and lung inflammation in animal models of SSc. Using a novel *in vivo* human skin challenge model of an innate immune response, we tested the effects of anabasum on inflammatory onset and resolution and compared it to prednisolone.

Methods: In this placebo-controlled study, subjects (N = 20) received placebo (n = 5), oral anabasum 5 mg BID (n = 5), anabasum 20 mg BID (n = 5), or prednisolone 15 mg QD (n = 5) for 4 days. On the 4th day, acute inflammation was triggered by intradermal injection of ultraviolet light-killed *E. coli* on both forearms of healthy subjects. Local inflammatory exudate was acquired from a suction blister raised at 4 hrs on one forearm (onset time point) and at 10 hrs on the contralateral forearm (resolution time point). Inflammatory exudate was analyzed for soluble mediators (chemokines, cytokines and lipid mediators) and immune cells. Blood flow to the site of inflammation was monitored by laser doppler.

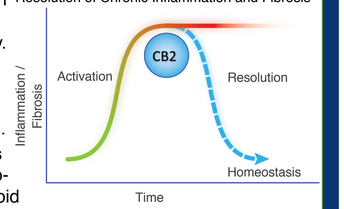
Results: Anabasum exerted a profound anti-inflammatory effect in this model by accelerating the resolution phase of the innate immune response. Anabasum: increased blood flow during the resolution phase at 10 hours; reduced IL-8 and neutrophils in blister exudate 10 hours post-challenge, as did prednisolone; reduced the proinflammatory lipid mediators LTB4, $PGF_2\alpha$, TxB_2 and PGE_2; increased the SPMs lipoxins (LXA_4, LXB_4) and resolvins (RvD1, RvD3, RvD5); and hastened bacterial clearance, whereas prednisolone slowed bacterial clearance during the resolution phase (resolution toxic).

Conclusion: Anabasum has novel pharmacologic effects on infection-induced innate immune responses as it exerts a striking anti-inflammatory effect leading to timely resolution of inflammation. This activity offers promise for anabasum in the treatment of SSc.

Background

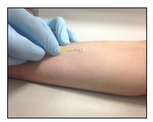
- Systemic sclerosis (SSc) is characterized by chronic activation of innate immune response. Progressive organ fibrosis and vascular damage result in chronic morbidity and high mortality. There are currently no FDA-approved therapies to stop fibrosis in SSc.
- The innate immune response is characterized in part by activation of the inflammatory response followed by resolution.
- Resolution is a complex physiological process, which includes the reduction of pro-inflammatory lipids and an increase in pro-resolving lipid mediators. CB2 receptors of the endocannabinoid system are found on activated immune cells and resolve inflammation via production of pro-resolving lipid mediators.
- Anabasum is a CB2 agonist able to target inflammation without immunosuppression. We are testing the ability of anabasum to activate resolution of inflammation and reduce fibrosis in humans.

Resolution of Chronic Inflammation and Fibrosis

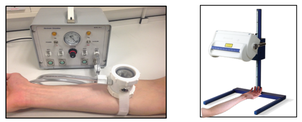


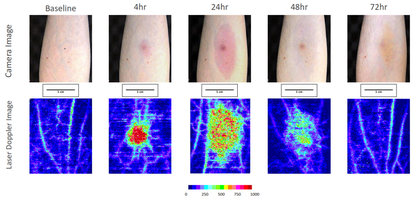
Methodology: Model System

1) Acute inflammation triggered by injection of UV light-killed *E. coli* on forearms of healthy volunteers

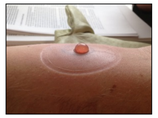


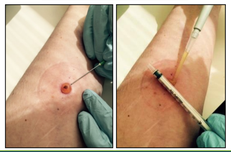
2) Inflammation followed by blister induction. Blood flow to inflammation site monitored by laser doppler imager (figure below)



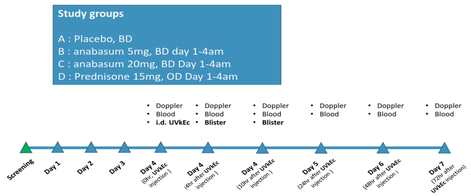


3) Induced blister exudates collected at 4 hours (peak of onset phase) and 10 hours (beginning of resolution phase) after challenge, which was analyzed for soluble mediators and immune cells.





Methodology: Trial Design

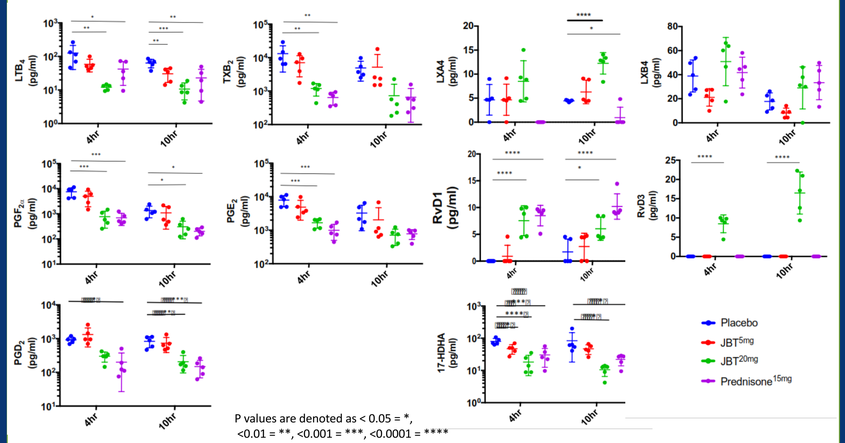


- 20 subjects were enrolled in the double-blinded clinical trial with the following breakdown:
  - Placebo: n = 5
  - Oral anabasum 5mg BID: n = 5
  - Oral anabasum 20mg BID: n = 5
  - Prednisolone 15mg QD: n = 5
- Subjects were dosed starting 3 days prior to challenge with killed *E. coli* and on the morning of day 4

Results

Pro-inflammatory lipid mediators

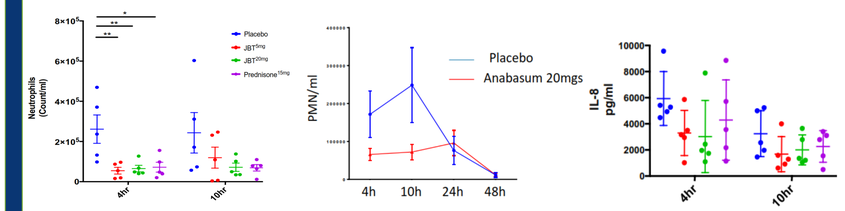
Pro-resolving lipid mediators



P values are denoted as < 0.05 = *, <0.01 = **, <0.001 = ***, <0.0001 = ****

Anabasum 20 mg BID > 5 mg BID caused a reduction in pro-inflammatory lipid mediators equivalent to 15 mg QD prednisolone.

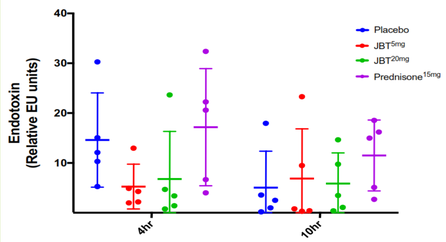
Anabasum 20 mg BID > 5 mg BID caused an increase in pro-resolving lipid mediators, greater than or equal to prednisolone.



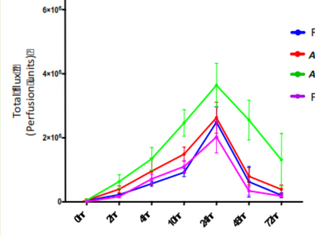
Anabasum 20 mg BID reduced accumulation of neutrophils and neutrophil chemokine IL-8 in the blister exudate at 4 and 10 hours post-challenge with *E. coli*, equivalent to prednisolone. p values are denoted as < 0.05 = *, <0.01 = **

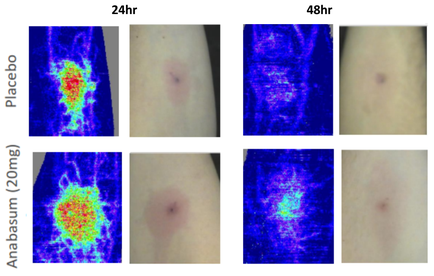
Results (continued)

Endotoxin clearance with anabasum



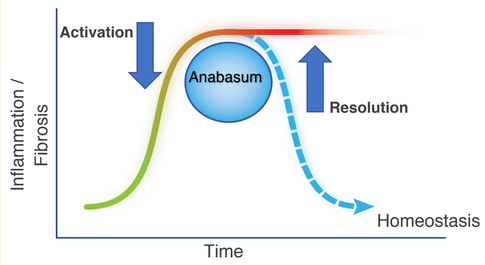
- Anabasum at 5 mg & 20 mg BID accelerated bacterial clearance to 4 hours post-challenge
- In contrast, prednisolone slowed bacterial clearance during the resolution phase (resolution toxic).





- Anabasum 20 mg BID increased blood flow to the site of inflammation during the resolution phase, starting 4 hours after challenge
- This is thought to help accelerate the restoration of tissue homeostasis

Conclusions



- Anabasum reduces the onset and accelerates the resolution phase of inflammation in humans.
- Anabasum 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 anabasum in the treatment of chronic rheumatic diseases.

Acknowledgments

A special thank you to all the volunteers for their participation in this study

This project was funded by Corbus Pharmaceuticals, Inc.

For clinical trial data with Anabasum, please see the following posters and presentations:

Systemic Sclerosis: **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

Dermatomyositis: **Werth et al., Poster # 7L**, A Phase 2 Study of Safety and Efficacy of Anabasum (JBT-101), a Cannabinoid Receptor Type 2 Agonist, in Refractory Skin-Predominant Dermatomyositis; 11/7, 9 – 11am;

Werth et al., Poster# 2156, Comparison of Patients with Dermatomyositis in a Specialty Clinic Versus Clinical Trial with Anabasum (JBT-101), a Cannabinoid Receptor Type 2 Agonist; 11/7, 9 – 11 am