Experimental Tendinopathy Treatment with SM04755, a Topical Small Molecule Inhibitor of the Wnt Pathway

Vishal Deshmukh, PhD, Timothy Seo, MS, and Yusuf Yazici, MD
Samumed, LLC, San Diego, CA

Background

- Tendinopathy is an inflammatory, degenerative, fibrotic condition, caused by injuries or overuse. It is characterized clinically by pain, swelling, and impaired performance.1,2
- Current therapeutic options address symptoms, and not underlying pathology, presenting an unmet medical need.3
- The Wnt pathway is upregulated in chronic tendinopathy and involved in inflammation, tenocyte differentiation, and fibrosis.4
- Samumed is developing SM04755, a small molecule Wnt signaling pathway inhibitor, previously shown to inhibit inflammation, reduce fibrosis and increase tenocyte differentiation in nonclinical models, as a potential topical therapeutic for the treatment of tendinopathy.5

Methods

- SM04755 was assessed in intra-tendon collagenase-induced rodent Achilles tendinopathy models. Tendinopathy was induced by collagenase injection (500 µg).
- In the acute dose response model, a single injection of collagenase or sham per animal on Day -4, followed on Day 0 by daily vehicle, 0.3 mg/cm², or 0.9 mg/cm² SM04755. Tendons were harvested on Days 7, 14, and 21.
- In the RIDT model, collagenase injections were given at Days -28 and -14, followed on Day 0 with daily vehicle or 0.3 mg/cm² SM04755. Achilles tendons were harvested on Days 7, 14, 21, and 28.
- Histological analyses were performed by blinded observers and tendons scored based on linearity, tendon cell shape, tendon cell density, inflammation, and hemorrhage (range 5-20).6
- Animal studies were approved by the Samumed, LLC Animal Committee and performed in accordance with the U.S. Department of Agriculture’s Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals.
- Statistical analyses: one-way ANOVA for multiple group comparisons and t-tests for two group comparisons.

Results

Tendon health scores after delayed SM04755 treatment in the collagenase tendinopathy model

![Histological images](image)

Figure 2. (a) Schematic of the delayed treatment tendinopathy model. (b) Histological scores of rat tendons from the RIDT model (left) and representative images of rat tendons stained with H&E (right). In the RIDT model, 0.3 mg/cm² SM04755 improved tendon health scores compared to vehicle at Day 21.

Conclusions

- In the acute model, the 0.9 mg/cm² SM04755 dose resulted in improved tendon health compared to vehicle at both Days 14 and 21. The 0.3 mg/cm² dose showed improvement at Day 21, indicating a dose-dependent speed of response.
- In the RIDT model, 0.3 mg/cm² SM04755 promoted tendon healing compared to vehicle at Day 21. There was no statistical difference at Day 28.
- Limitations of the collagenase model were absent fibrotic changes, allowing spontaneous healing in the vehicle group by Day 28, reducing effect size.
- SM04755 demonstrated accelerated improvement of tendon histology in acute and RIDT models compared to vehicle, suggesting that topicaly applied SM04755 has potential as a therapeutic intervention for tendinopathy.
- Studies in patients with clinical tendinopathy are planned.

References and Acknowledgements