Mitigating Pathologic Fibrosis following Volumetric Muscle Loss in a Porcine Model

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What was the question?
Volumetric muscle loss (VML) resulting from extremity trauma presents functional deficits and fibrosis, which ultimately manifest disability. The extensive fibrotic accumulation is expected to interfere with neural, trophic, vascular, and mechanical connectivity of any possible regenerative or rehabilitative approaches. It is possible that fibrosis following VML injury could be as much of a problem to VML injured patients as the loss of contractile tissue. Our objective was to quantify the muscle properties and stiffness following injury and investigated if the fibrotic deposition could be mitigated using an anti–fibrotic agent. We hypothesized that muscle stiffness would progressively increase following injury and that anti–fibrotic treatment could prevent the overwhelming fibrotic response.

How did you answer the question?
Female Yorkshire Cross pigs (n=10) were randomized to sham or a non–repaired ~20% VML injury to the peroneous tertius muscle. Immediately following surgery injured animals were further randomized to nintedanib (Ofev; 300 mg/day) or no treatment for 30 days. Analysis of muscle function via peroneal nerve stimulation, compartment volume, and quantitative muscle stiffness using Shearwave Elastograph was conducted longitudinally one month post–injury. Terminally comprehensive histopathologic, biochemical, and genetic investigations were conducted of the skeletal muscle and fibrosis.

What are the results?
to injury there was no difference in the maximal isometric torque (0.28 +\– 0.01 Nm/kg) across groups and the sham operated torque remained stable over time (p=0.23). Through one month post–VML, non–treated muscles presented a significant deficit (24%) in maximal torque compared to the sham operated ($p<0.01$). Additionally, anti–fibrotic treated muscles presented an even greater strength deficit (39%) compared to VML– uninjured pigs. The stiffness in the VML defect area increased significantly more (7–fold) in the VML–injured untreated leg than the anti–fibrotic treated pigs by one month post injury. Which was coupled with the non–repaired muscle having ~40% more collagen per mg of tissue than those receiving anti–fibrotic treatment (p=0.01).

What is your conclusion?
This work indicates that VML injury progressively induces fibrosis and muscle stiffness increases, in particular when the injury is left to follow its natural sequela. However, anti–fibrotic treatment can mitigate the pathologic development of fibrosis although isometric muscle strength remains impaired. Future work should evaluate optimal timing of anti–fibrotic treatment combined with regenerative medicine approaches in efforts to improve