Improving Response to Treatment for Patients with DDD with the use of the Fibronectin-aggrecan complex

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ABSTRACT INTRODUCTION: Protein biomarkers associated with lumbar disc disease have been studied as diagnostic indicators and therapeutic targets. A cartilage degradation product, the Fibronectin-Aggrecan complex (FAC) identified in the epidural space, has been shown to predict response to lumbar epidural steroid injection in patients with radiculopathy from herniated nucleus pulposus (HNP) and identified in patients with degenerative disc disease (DDD). A therapeutic agent that prevents the formation of the G3 domain of aggrecan will reduce the fibronectin-aggrecan G3 complex and accordingly may be an efficacious treatment. Since the production of G3 domain of aggrecan is catalyzed by different known classes of proteases, a common inhibitor of all of these proteases could be an ideal therapeutic agent. Such a protease inhibitor is found in plasma and synovial fluid, alpha-2-macroglobulin (A2M). This investigation attempted to determine the ability of FAC to predict response to biologic therapy with concentrated autologous A2M for patients with LBP from Degenerative Disc Disease (DDD).

METHODS: This study was a prospective cohort of 24 patients with low back pain and MRI positive for DDD. Outcome Measures included Oswestry disability index (ODI) and visual analog scores (VAS). They were noted at baseline and at 3- and 6-month follow-up. Primary outcome of clinical improvement was defined as patients with both a decrease in VAS of at least 3 points and ODI >20 points. All patients underwent lavage for molecular discography and delayed FAC analysis and injection of platelet poor plasma rich in A2M at the time of the intradiscal injection. Statistics using Anova with Bonferroni correction and Pearson correlation analysis was performed.

RESULTS: Patients with FACT-positive assays were significantly more likely to show improvement in their VAS and ODI at follow-up. Mean VAS improvement in FACT-positive patients was 4.9 +/- 0.9 and 4.0 +/- 1.0 at 3 and 6-months, compared to 1.5 +/- 1.2 and 2.3 +/- 1.3 in those with negative FACT ($p < 0.0001$). Similarly, ODI improved on average 37 +/- 9.3 and 28 +/- 14 points at 3- and 6-months in FACT-positive patients compared to 9.4 +/- 11.9 and 12.6 +/- 11.8 points at 3- and 6-months in FACT-negative patients ($p<0.0001$). Correlation analysis demonstrated that a FACT-positive test correlates with improvement in 3-month VAS (Pearson $r = 0.83$; $p < 0.0001$) and ODI (Pearson $r = 0.71$; $p<0.0001$) and 6-month VAS (Pearson $r = 0.58$; $p<0.0001$) and ODI (Pearson $r = 0.53$; $p<0.0001$). When a 20-point ODI improvement cut-off is applied, 77% of FACT+ patients and 27% of FACT-negative patients meet this strict definition of clinical improvement.

DISCUSSION: Patients who are "FAC+" within the disc are more likely to demonstrate clinical improvement following intradiscal autologous A2M injection. The results of this investigation suggest that autologous A2M may be an efficacious biologic treatment in discogenic pain and that FAC may be an important biomarker in patient selection for this treatment. We utilized a definition of clinical improvement that was in excess of the minimal clinically improved difference (MCID). Additionally, our defined outcome measure was a combination of two universally accepted outcome parameters (ODI and VAS). The current study provides evidence for a molecular biomarker that may improve patient selection and thus clinical outcomes in the treatment of discogenic back pain.

SIGNIFICANCE: This study demonstrates that a platelet poor autologous concentrate rich is A2M is likely to result in clinical improvement of LBP in patients who demonstrate the FAC in the suspected disc. This pilot study shows that a combination of diagnostic and therapeutic may be the 1st theranostic application for CLBP of discogenic origin.

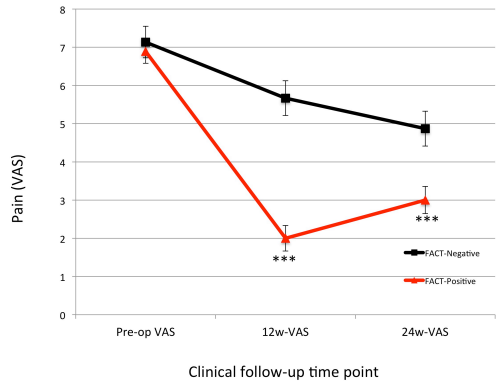

Fig.1. VAS at 12 and 24 weeks

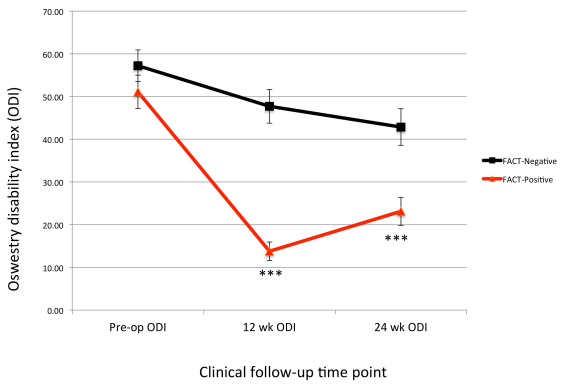

Fig 2. ODI at 12 and 24 weeks