HYPOTHESIS

Dupuytren's contracture is the most common inherited connective tissue disease in humans. A restrictive fibrosis and fibroblastic proliferation are hallmarks of the disorder. Myofibroblasts, a derived subset of fibroblasts especially important in scar formation and wound contraction, have been found at elevated levels in affected Dupuytren's tissues. Transformation of fibroblasts to myofibroblasts is characterized by expression of alpha smooth muscle actin (alpha-SMA) and increased production of extracellular matrix (ECM) components, both events of relevance to connective tissue remodeling.

We hypothesize that inhibition or reversion of myofibroblast phenotype to normal fibroblast would result in less contraction and fibrosis, and may become the basis of therapeutic intervention in the disease.

In the present study we propose that increasing the activation of the cyclic AMP (cAMP)/protein kinase A signaling pathway will inhibit transforming growth factor-beta1 (TGF-beta1)-induced ECM synthesis and myofibroblast formation and may provide a means to blunt fibrosis.

METHODS

Primary cultures of fibroblasts from DC patients derived from areas of Dupuytren's disease cord (DD cord), from adjacent and phenotypically normal palmar fascia (PF), and from palmar fascia from patients undergoing carpal tunnel release (CTR) were treated with TGF-beta1 (2 ng/ml) and forskolin (10 micro-M) (a known stimulator of cAMP). Total RNA was extracted and subjected to real time RT-PCR analysis.

RESULTS

Our initial findings show that basal mRNA expression levels of alpha-SMA, fibronectin- extra domain A (FN1-EDA), type I and type III collagen were all increased in DD-cord and in PF-derived cells compared to CTR-derived fibroblasts. We also show that this increase was further augmented by stimulation with TGF-beta1 in DD-cord derived fibroblasts. Furthermore, we demonstrate that increase in alpha-SMA and FN1-EDA levels by TGF-beta1 in DD-cord derived fibroblasts was greatly suppressed by addition of forskolin (Figure 1). Additionally, we observed a substantial increase in connective tissue growth factor (CTGF) in DD-cord derived fibroblasts when stimulated with TGF-beta1, and this increase too was greatly reduced by addition of forskolin (Figure 2).

SUMMARY POINTS

- These studies raise the prospect of using stimulation of cAMP as a means of treating Dupuytren's contracture, as increased cAMP levels show potential to inhibit the formation of myofibroblasts and accumulation of ECM components.
- Further studies are in progress to confirm these changes at the protein level and to confirm the functional significance of the effect of elevated cAMP on DD-cord derived fibroblasts.

Figure 1

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PAPER 54

Saturday, October 9, 2010 • 8:42-8:48 AM
Paper Session 6: Radius Volar Plating and Dupuytren’s Disease

An Economic Analysis of Fasciectomy, Needle Aponeurotomy, and Collagenase Injection for Dupuytren’s Contracture

Level 2 Evidence

- Neal C. Chen, MD
  Melissa J. Shauver, MPH
  Kevin C. Chung, MD

HYPOTHESIS

An economic analysis has not been performed to critically evaluate the various treatments for Dupuytren’s contracture. We undertook a cost-utility analysis to compare traditional fasciectomy with needle aponeurotomy and collagenase injection, two new treatments. We hypothesize that these two less invasive treatments are dominant strategies in the initial treatment of Dupuytren’s contracture.

METHODS

An expected value decision analysis model was constructed with three primary arms: (1) partial open fasciectomy, (2) needle aponeurotomy, and (3) collagenase injection. A survey was administered to a cohort of fifty subjects aged 50 to 70 to determine the utilities of the different interventions. These utilities were coupled with the expected years of life left to calculate quality-adjusted life years (QALYs) for a 63-year-old male afflicted with Dupuytren’s contracture. For each treatment arm, Medicare cost data were used to derive the cost per each additional QALY gained over no treatment. Probabilities of clinical outcomes were derived from a systematic review of the highest level of evidence studies for each intervention.
The analysis was performed using TreeAge decision analysis software. Multiple sensitivity analyses were conducted to assess the impact of varying the rate of revision fasciectomy and rates of complications in each arm of the analysis. Cost of collagenase was varied through a wide cost range. The threshold for a cost-effective treatment is based on the traditional willingness-to-pay of $50,000 per QALY gained.

RESULTS
The cost of open partial fasciectomy was $820,114 per QALY gained over no treatment. The cost of needle aponeurotomy was $96,474 per QALY gained versus no treatment. When a sensitivity analysis was performed and the success rate was set at 100%, the cost per QALY of needle aponeurotomy was $49,631.

When a complete collagenase injection series was priced at $250, the cost was $31,856 per QALY gained. When the injection series was priced at $250 and the injection was unsuccessful, but revision open fasciectomy was successful, the cost was $53,392 per QALY gained. When the injection series was priced at $945, the cost was $49,995 per QALY gained. At the market price of $5,400 per injection series, the cost was $166,268 per QALY gained.

SUMMARY POINTS
- Cost-utility analysis is dominated by the limited cost-effectiveness of primary and revision open partial fasciectomy.
- Needle aponeurotomy is cost effective only if the rate of clinical success is 100%.
- Collagenase injection is cost effective when priced below $945 per injection series.

REFERENCES

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PAPER 55
Saturday, October 9, 2010 • 8:48-8:54 AM
Paper Session 6: Radius Volar Plating and Dupuytren’s Disease

Analysis of Efficacy and Safety of Treatment with Collagenase Clostridium Histolyticum among Subgroups of Patients with Dupuytren’s Contracture

Level 1 Evidence

- Raymond B. Raven, MD
- Harvey Kushner, PhD
- Dat Nguyen, PharmD

HYPOTHESIS
Three different randomized, placebo-controlled, double-blind phase 3 trials have been conducted to examine the safety and efficacy of treatment with collagenase clostridium histolyticum (CCH, XIAFLEX) for patients with Dupuytren’s contracture. We tested the hypotheses of no differences in outcomes or adverse events (AE) among subgroups of patients actively treated with CCH stratified by age, gender, diabetes and obesity.

METHODS
Patients with joint contractures of >=20 degrees in the metacarpophalangeal (MP) or proximal interphalangeal (PIP) joints received 0.5mg of CCH per injection. A treatment cycle consisted of injection, manipulation the following day, and a 30 day follow-up visit with a maximum of 3 cycles depending on achievement of clinical success (defined primary endpoint of reduction in contracture down to 0-5 degrees of normal). Statistical analyses included the Fisher’s Exact Test to compare clinical success rates by gender and diabetes status and the Cochran-Armitage Trend Test to determine trends in clinical success rates for age and body mass index (BMI).

RESULTS
Across the 3 trials, active treatment with CCH was received by 271 subjects. The table below shows the clinical success rates (%) after the last treatment cycle among CCH treated subjects for MP and PIP joints, together and separately. The mean ± SD for age was 62.2 ± 9.2 years (range: 33-89). There was no statistically significant trend in clinical success rates by age for all joints (P=0.59), MP (P=0.06) or PIP (P=0.89). Analysis of BMI (mean ± SD = 26.5±3.9 kg/m2) by 3 categories (<25, 25-29.99, 30+) also showed no statistically significant trends in clinical success rates for all joints (P=0.99), MP (P=0.25) and PIP (P=0.66). There were no statistically significant differences in clinical success rates among patients with a reported medical history of diabetes vs. non-diabetics for all joints (P=1.0), MP joints (P=1.0), and PIP joints (P=1.0). Females did as well as males for all joints (P=0.30), MP joints (P=0.08) and PIP joints (P=0.34).

A total of 594 injections of CCH were administered. Overall, over 95% of the patients reported at least one treatment-related AE. The six most common AEs (>=25%) were edema peripheral, contusion, injection site hemorrhage, injection site pain, upper-extremity pain, and injection site swelling. No differences in AE profiles were found with age, BMI, diabetes or gender.