EMERGING TECHNOLOGIES

COLLAGENASE
A biologic nonsurgical Treatment for Dupuytren’s Contracture

Collagenase Clostridium Histolyticum for the Treatment of Dupuytren’s Contracture

The Scientific Evidence

Collagenase Injection for Dupuytren’s Contracture
Conflicts

Paid consultant to Auxilium
Involved in some Clinical trials

Dupuytren's Disease Reappraisal

Despite Over 200 yrs Scientific study
Despite Over 2700 Publications Since 1900
Despite Understanding
the Clinical Presentation

The Cause and The Cure
Remain Elusive
Collagen Mechanics

Nodules

Histology

Nodules are dense, fusiform, hypercellular, hypervascular masses of tissue smaller than clinical nodules and typically not palpable.

Increased cellularity within diseased tissue predicts an increase in recurrence rates up to 50%.

Type I to Type III
Collagenase is an enzyme derived from Clostridium hystolyticum. Purified by column chromatography, reconstituted with a sterile diluent of calcium chloride.

Larry Hurst MD
Evidence Based Medicine

“the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”

D.L. Sackett

Nolo Non nocere

Minimize patient harm
Clinical decisions
Based on evidence least likely to be wrong

Papers that evaluate each technique

Contracture success rates, Recurrence rates, Complications
Evidence Shortcomings

The definition of success and recurrence are inconsistent.
Accuracy of contracture measurement
No study on patient satisfaction and disability
No randomized comparative studies of Collagenase with LF or NA.

Dynamic Flexion Contracture

Cord crosses MCP and PIP joints
Flexing one joint allows extension of the other
Also position of CMC joints

MCP joint contractures are easier to correct and less likely to recur than PIP joint

The prognosis is worse if more than one ray is involved.
The small finger PIP joint worse prognosis than other finger PIP joint

PIPJ Contracture of More Than 60° a bad actor

Improvement in the PIPJ contracture greater correlation with hand function than an improvement in the MCPJ contracture

Collagenase treatment is the only treatment with LEVEL I data

FDA regulated, random double blind, placebo controlled clinical trials using collagenase

Clinical Studies: Design and Inclusion Criteria

Two randomized, double-blind, placebo-controlled studies of XIAFLEX 0.58-mg injections

Contracture of at least 1 finger (other than the thumb) with a palpable cord

<table>
<thead>
<tr>
<th>Contracture Location</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP joint contracture</td>
<td>20° to 100°</td>
</tr>
<tr>
<td>PIP joint contracture</td>
<td>20° to 80°</td>
</tr>
</tbody>
</table>

Positive table top test

CORD
Collagenase Option for Reduction of Dupuytren
Clinical Studies: Methods

Exclusions
- Surgical treatment on the selected primary joint within 90 days before the first injection
- Anticoagulation medication (except for up to 150 mg of aspirin per day) within 7 days before first injection

Treatment
- Up to 3 injections of XIAFLEX or placebo in the cord affecting the selected joint
- Injection administered on days 0, 30, and 60
- Approximately 24 hours after each injection, investigator facilitated rupture of cord (finger extension procedure) if needed
- Assessments were made 30 days after the last injection

Clinical Studies: Endpoints

Primary
Reduction of the contracture to within 0° to 5° of normal
30 days after the last injection (30, 60, or 90 days)

Selected Secondary
Mean increase in range of motion from baseline in degrees

Results reported for all joints, MP, and PIP joints
In XIAFLEX-treated patients, the mean (±SD) number of injections given to the cord associated with the contracture was 1.7 (±0.8) in the 90-day controlled period in each trial

Clinical Studies: Patient Characteristics

<table>
<thead>
<tr>
<th>CORD-I*</th>
<th>CORD-II*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients with prior surgery for Dupuytren’s contracture</td>
<td>38%</td>
</tr>
<tr>
<td>Proportion of patients with prior surgery for Dupuytren’s contracture on the same finger as the primary joint</td>
<td>8%</td>
</tr>
<tr>
<td>Mean number of affected joints</td>
<td>3.0</td>
</tr>
</tbody>
</table>

CORD-1 study  Hurst et al. NEJM 361, 2009
CORD-2 study  Australian Coleman et al J Hand Surg 2010
CORD-I*: Primary Endpoint Results by Treated Joint

Reduction of MP and PIP Joint Contracture to within 0° to 5° of Normal 30 Days After the Last Injection†

<table>
<thead>
<tr>
<th>Treated Joint</th>
<th>XIAFLEX</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP Joints</td>
<td>77%</td>
<td>7%</td>
</tr>
<tr>
<td>PIP Joints</td>
<td>64%</td>
<td>7%</td>
</tr>
<tr>
<td>All Joints</td>
<td>64%</td>
<td>7%</td>
</tr>
</tbody>
</table>

† After up to 3 injections. All comparisons with placebo were significant.

CORD-II*: Increase in Range of Motion

Mean Increase in Range of Motion From Baseline

<table>
<thead>
<tr>
<th>Joint Location</th>
<th>Baseline (XIAFLEX)</th>
<th>Post-treatment (XIAFLEX)</th>
<th>Baseline (Placebo)</th>
<th>Post-treatment (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP Joints</td>
<td>40°</td>
<td>41°</td>
<td>41°</td>
<td>47°</td>
</tr>
<tr>
<td>PIP Joints</td>
<td>80°</td>
<td>73°</td>
<td>76°</td>
<td>54°</td>
</tr>
<tr>
<td>All Joints</td>
<td>41°</td>
<td>47°</td>
<td>44°</td>
<td>54°</td>
</tr>
</tbody>
</table>

n=69 | n=34 | n=103

CORD-II: Increase in Range of Motion

<table>
<thead>
<tr>
<th>Joint</th>
<th>Baseline (XIAFLEX)</th>
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</tr>
<tr>
<td>All Joints</td>
<td>41°</td>
<td>47°</td>
<td>44°</td>
<td>54°</td>
</tr>
</tbody>
</table>

n=203 | n=133 | n=70

Cord II study

<table>
<thead>
<tr>
<th>Joint Location</th>
<th>Collagenase</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Joints</td>
<td>65.0</td>
<td>9.1</td>
</tr>
<tr>
<td>MCP</td>
<td>44.4</td>
<td>4.8</td>
</tr>
<tr>
<td>PIP</td>
<td>28.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

P < .001 | P = .003 | P = .009

n=45 | n=20 | n=25

Mean Range of Motion, degrees

Baseline
Post-treatment
(XIAFLEX)
Placebo
Post-treatment
(Placebo)
Range of motion improved on average 41° for MCP joints and 29° for PIP joints.

Overall, 94.0% of MCP joints and 67.1% of PIP joints showed some clinical improvement.

Up to 3 injections at 30-day intervals.

Primary endpoint - 5° extension deficit or less.

Stratified by severity of the initial joint disease:

- MCP contracture ≤ 50°: 88% met primary endpoint
- MCP contracture ≥ 50°: 57% met endpoint
- PIP contracture ≤ 40°: 81% met primary endpoint
- PIP contracture ≥ 40°: 22% met endpoint.

The CORD studies are the largest prospective, placebo-controlled studies conducted in patients with Dupuytren's disease to date.

My Indications for use

- Isolated MCPJ contracture
- 2 finger MCPJ contracture with Y cord
- PIPJ contracture ≤ 40°
- Dupuytren patients with Co-Morbidities
- Patient Driven
Dosage and Administration

Reconstitute and inject based on the type of joint contracture to be treated to reach the recommended dose of 0.58 mg per injection.

Volumes Needed for Reconstitution and Administration

<table>
<thead>
<tr>
<th></th>
<th>Reconstituted XIAFLEX solution to be injected*</th>
</tr>
</thead>
<tbody>
<tr>
<td>For a cord affecting a metacarpophalangeal (MP) joint</td>
<td>0.39 mL</td>
</tr>
<tr>
<td>For a cord affecting a proximal interphalangeal (PIP) joint</td>
<td>0.31 mL</td>
</tr>
</tbody>
</table>

No Local anesthesia
- Ultrasound
- Move flexor tendon

Injection technique

Manipulation
- Local Anesthesia
- Wrist flexed
- No more than 3 tries

Day 2
- ? Extend 3-7
Double correction can occur with just a single injection of one cord. A single cord can cause contracture of 2 joints, or because of connections between cords MCPJ & PIPJ of same finger or adjacent MCP joints.

**Post-manipulation**

Nighttime MCP extension splint
ADL as tolerated
No Forceful Grip 4 weeks

**PIPJ Therapy**
Does Collagenase Injection Disrupt or Digest the Dupuytren’s Cord? A Magnetic Resonance Imaging Study.

Wolfe, 2012

5 patients MCP contracture

Cord disruption without injury to surrounding soft tissue structures by clinical and imaging criteria. There is a significant increase in signal intensity within the cord demonstrating disorganization of collagen, not seen in the tendons. Statistically significant decrease in cord volume by MRI indicating a reduction in diseased tissue rather than simple cord division.

Axial MRI image demonstrating appearance of Dupuytren’s cord before (left) and after (right) injection with collagenase and manipulation.

Coronal MRI image demonstrating appearance of Dupuytren’s cord before (left) and after (right) collagenase injection and manipulation.

Badalamente, Hurst, 2011 Cord I data

Recurrence was defined as 20 degree contracture.
Mean 3.9 years FU

Stonybrooke center site 35 patients
MP joints 4/28 recurred (14%)
PIP joints 6/26 recurred (23%)
overall recurrence rate was 18.5%
61/448 MP joints recurred (13%)
58/170 PIP joints recurred (34%)
overall rate of 19.3%.

8 year FU
Hentz, J Hand Surg 2010

Initial evaluation of long-term recurrence rates suggests disease recurrence or progression in:
- 4 out of 6 patients with MCP contractures
- 2 patients with PIP contractures

Recurrence was generally less severe than the initial contracture in the MCP group
Patient satisfaction was high
3 year Recurrence rates

Averaged from studies with 3 yr FU

- Collagenase
- NA
- Dermatofasciectomy
- Fasciectomy

Adverse Reactions Occurring in ≥ 5% of XIAFLEX-treated Patients and at a Greater Incidence than Placebo in the Placebo-Controlled Trials Through Day 90 After Up to 3 Injections

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>XIAFLEX (n=249)</th>
<th>Placebo (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse reactions</td>
<td>98%</td>
<td>51%</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>73%</td>
<td>5%</td>
</tr>
<tr>
<td>Contusion</td>
<td>70%</td>
<td>3%</td>
</tr>
<tr>
<td>injection site hemorrhage</td>
<td>38%</td>
<td>3%</td>
</tr>
<tr>
<td>injection site reaction</td>
<td>35%</td>
<td>6%</td>
</tr>
<tr>
<td>pain in extremity</td>
<td>35%</td>
<td>4%</td>
</tr>
<tr>
<td>tenderness</td>
<td>24%</td>
<td>0%</td>
</tr>
<tr>
<td>injection site swelling</td>
<td>24%</td>
<td>6%</td>
</tr>
<tr>
<td>pruritus</td>
<td>15%</td>
<td>1%</td>
</tr>
<tr>
<td>lymphadenopathy</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>skin laceration</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>lymph node pain</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>erythema</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>axillary pain</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

81% of local reactions resolved without intervention within 4 weeks of XIAFLEX injections

Adverse reaction profile was similar for each injection regardless of the number of injections administered

However, the incidence of pruritus increased with more injections
Adverse Effects

The most frequently reported adverse drug reactions (≥ 25%) in the XIAFLEX clinical trials and at an incidence greater than placebo included:

- Edema peripheral (mostly swelling of the injected hand, 73% vs. 5%)
- Contusion (70% vs. 3%)
- Injection site hemorrhage (38% vs. 3%)
- Injection site reaction (35% vs. 6%)
- Pain in the treated extremity (35% vs. 4%)

Localized Edema
Peripheral

PIPJ with 60° contracture
Skin tear & extension post release

- One week post release
  - Skin tear healing
  - Residual contracture & extensor attenuation apparent (discrepancy between active and passive ROM)

DIPJ flexion exercise with PIPJ straight for ORL tightness
MCPJ flexion with IPJs straight and reverse blocking for PIPJ extension exercises

5 weeks post injection
During clinical studies, patients with Dupuytren’s contracture were tested at multiple time points for antibodies to the protein components of XIAFLEX.

- 30 days after the first injection of XIAFLEX 0.58 mg

- 92% of patients had antibodies detected against AUX-I
- 86% of patients had antibodies detected against AUX-II
1,082 patients received XIAFLEX 0.58 mg in controlled and uncontrolled studies (2,630 XIAFLEX injections total). 3 patients had a flexor tendon rupture of the treated finger within 7 days of injection. Other XIAFLEX-associated serious local adverse reactions included:
- Pulley rupture
- Ligament injury
- Complex regional pain syndrome
- Sensory abnormality of the hand

This puts the overall incidence of tendon rupture at around 0.5%. Palmar fasciectomy carries a similar incidence of injury to the flexor tendon (0.2%), according to a study by Loos 2007.

Distance between the skin and the flexor tendon averages 7 mm at the MCP joint and 4 mm at the PIP joint, and the bevel of a standard 27-gauge needle is approximately 1.3 mm.
**Small Finger**

- 4 mm at the PIP joint
- 7 mm at the MCP joint

**SAFE ZONE**

- Place needle PARALLEL to cord
- Center to side
- Palmar digital crease

**Complications**

<table>
<thead>
<tr>
<th>Fasciectomy</th>
<th>Needle Aponeurotomy</th>
<th>Collagenase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve injury</td>
<td>Skin tear</td>
<td>Swelling, bruising</td>
</tr>
<tr>
<td>Vessel injury</td>
<td>Nerve injury</td>
<td>Skin tear</td>
</tr>
<tr>
<td>Loss of flexion</td>
<td>Lymph node pain</td>
<td>Tendon and pulley rupture</td>
</tr>
<tr>
<td>Stiffness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue Necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRPS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Not all complications are equal

Last 2 years repaired
7 digital nerve lacerations
Post NA
2 Legal suits

“A cut worm forgives the plough”
A cut nerve energizes the Lawyer

Cost

Chen, J Hand Surg, 2011

Fasciectomy | Needle Aponeurotomy | Collagenase

Facility | Surgeon | Surgeon | Drug

Needle | Needles | Needles

Surgeon | Anesthesia | Surgeon | Drug

Surgeon | Surgeon | Surgeon

Cost Utility Analysis

Chen, J Hand Surg, 2011

Level II

If tx successful with disease free interval

Fasciectomy $820,114 / QALY
NA $96,474 / QALY in office
COLL $49,995 / QALY @ $945
$166,268 / QALY @ $5400
Simpler treatment
Less down time
Minimally invasive
No complications
Long disease Free Interval

Downtime

NA, Collagenase 1-2 weeks
Fasciectomy 8-12 weeks

We Believe XIAFLEX Is a Paradigm Changing Treatment

Pre XIAFLEX injection
30 days following XIAFLEX injection

• Simple, non-invasive injection of XIAFLEX
• Established mechanism of action and selective for specific types of collagen
• XIAFLEX’s post-approval profile is consistent with clinical trial experience

Advertising Influence
Future Questions

Multiple injections @ same setting, same or opposite hand
Timing of Manipulation
Therapy protocol for the PIPJ contracture
Use in collagen disorders adhesive capsulitis
Use in Peyronies

Surgeon Bias

Discuss the options

Summary

Collagenase is an approved and viable treatment of adult patients with Dupuytren’s contracture with a palpable cord
It is efficacious
It is safe with rare complications involving collagen structures like tendons and pulleys
It has a high patient satisfaction rate
Recurrence rates are higher fasciectomy and probably slightly lower than Needle Aponeurotomy
Modified McCash Technique for Dupuytren’s Release

Joseph Imbriglia, MD
Rafael J. Diaz-Garcia, MD

Fig. 14.11 From left: proximal, superficial and central displacement of the neurovascular bundle with increasing flexion contracture at the proximal interphalangeal joint.
Fasciectomy. Unfortunately free grafts on the palm of the hand, even of full thickness as advocated by Kanavel et al. (1929), are not as satisfactory as those applied to the flexor aspect of the knee or elbow. In the first place, it is difficult in the palm to prevent serous effusion or haematoma and also in Dupuytren's contracture the graft is inserted to skin which is reduced in vitality by disease and by the direction it may have been present. If the graft does not take, re-operation is required.

• 1961 – CR McCash described technique at meeting Scandinavian Club for Hand Surgery
• 1964 – “The Open Palm Technique in Dupuytren's Contracture”
Dupuytren’s Contracture

Treatment choices - 2014
- collagenase injection
- needle aponeurectomy
- fasciectomy
- STSG or cross finger flaps in severe cases

Fasciectomy

Techniques
- straight incision with z-plasties
- Bruner incision with v-y advancement flaps
- transverse incisions in palm and fingers leaving wounds open
- transverse incisions using FTSGs to close wounds

Dupuytren’s Disease – My Approach

Fasciectomy
- never complete
- transverse incision in palm (Mc Cash technique)
- either transverse or Bruner incisions in fingers
- leave palm open
• Do not attempt to remove all fascia

• Make transverse incisions through the fascia

Case 1

70 yo male, right hand Dupuytren’s involving MF, RF, and SF
comfortable dressing with fingers in position of function

dressing change at 3-4 days post op

ROM of all joints--- act & passive

sutures out at 10 days

at all costs avoid tight dressings, swelling and severe pain

the combination of pain and swelling can result in RSD like picture
Case 2

50 yo with Dupuytrens diathesis
Case 3

42 yo with Dupuytren’s diathesis
Recurrent Dupuytren’s Disease

Watson and Lovallo, 1987
- 11 patients with 14 PIP joint arthrodesis
- 11 small fingers; 3 ring fingers
- Average follow-up = 4 yrs

Criteria for arthrodesis:
- Loss of 1 or both digital artery or nerve
- Severe palmar scarring from previous surgery
- Flexion contracture > 70°

Recurrent Dupuytren’s Disease

Roush and Stern, 2000
- 19 patients (28 fingers)
- Median follow-up = 4 years
- 17 of 28 recurrences involved small finger

3 Groups
- Limited fasciectomy / interphalangeal arthrodesis (7)
- Dermatofasciectomy and FTSG (8)
- Fasciectomy and local flaps (13)
Recurrent Dupuytren’s Disease

Jensen, 1993

- 23 finger amputations (19 patients)
- 17 small fingers and 6 ring fingers
- Mean follow-up = 4 years

- Recurrent lack of extension in 9 out of 16 finger amputations distal to MCP joint

- Painful neuroma/phantom limb pain in 5 out of 7 little finger amputations through or proximal to the MCP joint.

- When amputation in the little finger is necessary, disarticulation of the MCP joint preferable to amputation at more distal level.

General Principles

In defects place either FTSG or cross finger flaps when necessary

Case 4
48 y/o male with hx of Dupuytren’s Contracture s/p fasciectomy x 2 with FTSG approximately 10 years prior
McCash Technique Summary

- small transverse incisions in palm & fingers
- leave palm open
- large defects in fingers can be grafted
- in recurrent disease with skin loss/contracture a cross finger flap may be necessary

Thank You