Collagenase Clostridium Histolyticum (CCH) for Peyronie’s: An Update

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Peyronie’s Disease: Psycho-sexual disorder

Background

• Scarring/plaque of the tunica albuginea with excessive abnormal collagen deposition\textsuperscript{1}

• Potential symptoms\textsuperscript{2}: penile curvature/deformity, pain, shortening, or indentation, erectile dysfunction, difficulty with sexual intercourse, loss of self-esteem and depression

• In literature estimated prevalence for adult men of 5\%\textsuperscript{1}; average age of disease onset is 53 yrs\textsuperscript{1}

• Higher association with conditions such as diabetes, erectile dysfunction and others\textsuperscript{2}

• Surgery is typically the treatment of last resort, but most patients are initially treated with FDA unapproved, and unproven medical therapies

\textsuperscript{1} Bella A, Peyronie’s Disease J Sex Med 2007;4:1527-1538

\textsuperscript{2} Nyberg L, J Urol. 128 48, 1982
Pathogenesis
Matrix Biology: What Is Collagen?

- Primary extracellular structural component
- All collagens contain a triple helix:
  - Composed of three polypeptide chains
  - Contains Gly-X-Y motifs (X and Y normally proline or hydroxyproline)
- The triple helix
  - Requires extensive post-translational modification ("hard to make")
  - Is extremely stable ("hard to break")
Collagen Remodeling:
The Net Result of Deposition and Degradation

- Both processes are highly regulated
- The process that predominates determines the outcome
- The predominant process is determined by the tissue environment

Collagen Degradation
(Digestion + Phagocytosis)
Predominance = poor wound healing, tumor metastasis

Collagen Deposition
(Synthesis + Stabilization)
Predominance = fibrosis
Collagen Degradation

- Degradation is a three step process:
  - Binding to collagen
  - “Unwinding” of triple helix (exposes cleavage sites)
  - Cleavage of collagen peptides

- Collagenase = enzyme that can effectively do all three steps

- Two classes of mammalian enzymes are true collagenases:
  - Some matrix metalloproteinases (MMPs)
  - Cathepsins K and L
Collagen Cleavage Differences  
(Clostridial vs. Mammalian)

**Clostridial collagenase**
- Fibrillar collagen types in vivo
- Cleaves multiple sites
- Relatively fast cleavage
- More complete degradation  
  (degrades fragments)

**Mammalian collagenases**
- All collagen types in vivo
- Cleaves only one site
- Relatively slow cleavage
- Incomplete degradation  
  (not all degrade fragments)

In both cases, resulting peptide fragments are rapidly cleared by non-specific proteases/gelatinases and/or phagocytosis.
Collagenase in Peyronie’s Plaque & tunica albuginea

- First report on use of collagenase to treat fibroproliferative disorders

- Initial studies evaluated time and dose responses:
  - Surgical specimens of excised plaque & normal tunica were weighed and incubated in buffer containing 400U of collagenase (time response)
  - Samples collected hourly for 12 h and also at 24 and 48 h
  - Extent of digestion evaluated by amino acid release to buffer (ninhydrin) and weight loss in remaining tissue
  - Time response experiments: Normal pericardium (autopsy specimen) injected with varying doses (10-400U) and incubated for 24h
  - Extent of digestion in pericardium determined by comparing the radius of the affected tissue to the size of the initial “bleb” resulting from injection

Gelbard et al, 1982
Collagenase Injection into Tunica Albuginea
Collagen lysis is confined to the injection site

- Injection into dorsal tunica (400 U clostridial collagenase in 0.2 mL)
- Incubation for 24 h before tissue processing
- Localized complete lysis of collagen (note sharp demarcation from normal tissue)

Gelbard et al. (1982), Urol Res 10: 135-140
Collagen Digestion in Peyronie’s Plaque

Gelbard et al. (1982), Urol Res 10: 135-140
Collagenase in Normal Tissues

- Additional studies:
  - Surgical specimens of excised plaque & autopsy specimens of normal tunica and corpus cavernosum injected with collagenase (400U)
  - A single dose of 600 U was injected adjacent to the femoral nerve of a rat (to evaluate in vivo effects)
  - Injected tissues were incubated in buffer for 24h and then evaluated histologically

- Results were the same in all tissues:
  - Lysis focal & well circumscribed (approximated volume of injection)
  - Only collagen affected (no effects on elastic fibers, nerves & blood vessels)
  - Substantial disruption of the injected plaques, & sig decrease in size

Gelbard et al. (1982), Urol Res 10: 135-140
Collagenase Injection into Peyronie’s Plaque
Complete disruption of plaque collagen

- Surgically excised plaque bisected:
  - Half was treated with collagenase (400 U in 0.1 mL)
  - Half was injected with saline (0.1 mL)
- Incubation for 24 h before tissue processing
- Note difference in size & morphology (both are same magnification)

Gelbard et al. (1982), Urol Res 10: 135-140
Therapeutic Uses of Collagenase
Translation from in vitro to the clinic

- Studies in surgically excised tissues used for proof of concept, characterization of pharmacology and clinical dose setting

- Examples:
  - Translation in Peyronie’s disease (Gelbard et al, 1982)
  - Translation in Dupuytren’s disease (Starkweather et al, 1996)
  - Translation between collagenase sources (Del Carlo et al, 2009)

Gelbard et al. (1982), Urol Res 10: 135-140, Tissue section courtesy of Dr. M. K. Gelbard
Dupuytren’s Contracture
Collagenase in Dupuytren’s Cord Explants

• Study used clostridial collagenase injected into surgically harvested Dupuytren’s cord
  • Tissues injected with 0, 150, 300 or 600 U collagenase & incubated for 24 hours (dose response)
  • Additional pieces injected with 0 or 3600 units & incubated for 24 hrs
  • All tissues placed into a mechanical testing device & loaded until failure
    • Stress to failure force calculated for the dose response experiment
    • Stress to failure force and stress-strain relationship (‘tensile modulus’) determined for the 3600 U sections
  • Tissues harvested and processed for histology (hematoxylin and eosin, also picrosirius red stain for collagen integrity)

Starkweather et al, 1996
PD Treatment Options

• Spontaneous resolution

• Oral therapy - Vitamin E, PABA, Colchicine, Tamoxifen

• Intralesional injection therapy
  • Calcium channel blockers (Verapamil)
  • Interferon (IFN)
  • Collagenase (Xiaflex) – FDA approval Dec 6, 2013

• Surgical options
  • Plication of contralateral corpora (Nesbit principle)
  • Incision & grafting (I & G) procedures
  • Prosthesis option with modeling or ancillary procedures
Intralesional Injection Therapy

Intralesional Injection Therapy

XIAFLEX Mechanism of Action
Collagenase Clostridium Histolyticum (Xiaflex) as a Minimally Invasive Rx for PD

- Double-blind, placebo-controlled Phase 2 study of safety & efficacy of 0.58 mg of AA4500 in subjects with PD
- Up to 3 treatment cycles (2 x 3)
  - 6 weeks between each cycle
- 136 intended PD subjects:
  - 182 screened
  - 147 randomized
  - Powered for penile curvature
- 12 investigator sites (US): August 2008 – October 2009
AUX-CC-801: Study Design

Prior to first dose, subjects were randomized by degree of penile curvature: 30 - 60 and 61 - 90

Randomized into 4 treatment groups to receive in a 3:1 ratio either AA4500 or placebo and in a 1:1 ratio penile plaque modeling or no modeling

Penile Plaque Modeling: AA4500 (51): Placebo (17)
No Penile Plaque Modeling: AA4500 (51): Placebo (17)

AA4500 0.58 mg in volume of 0.25 mL

2 doses per cycle up to 3 cycles, each 6 weeks apart
PDQ PD Symptom Bother Domain

| PDQ PD Symptom Bother Domain Questions¹* |
|-----------------|---------------------------------------------------------------|
| Q10.            | Thinking about the last time you had an erection, how bothered were you by any pain or discomfort you may have felt in your erect penis? |
| Q11.            | Thinking about the last time you looked at your erect penis, how bothered were you by the way your penis looked? |
| Q13.            | Thinking of the last time you had or tried to have vaginal intercourse, how bothered were you by your Peyronie’s disease? |
| Q15.            | How bothered are you with having vaginal intercourse less often? |

¹Q12 and Q14 (not shown) are “yes/no” screening questions and are not scored.

•PDQ PD symptom bother domain consists of 4 scored items and 2 “yes/no” questions that are not scored

•PD symptom bother severity is measured on a 5-point, Likert-type response scale
  -0 (not at all bothered) to 4 (extremely bothered)

•Score for the PD symptom bother domain is calculated as the sum of all responses and ranges from 0 to 16

AUX-CC-801: Endpoints

- Degree of penile curvature
- Peyronie’s PRO questionnaire (PDQ)
- Penile plaque measurements
- Penile length
- IIEF questionnaire
- Peyronie’s disease symptomatology
AUX-CC-801: Demographics

• Mean age/mean duration of disease
  - 56.6 years/2.8 years

• Mean penile curvature
  - 53.5 degrees
  - 70% were ≤ 60 degrees

• Plaque
  - 55% had no calcification
  - 45% had non-contiguous stippling
  - Mean length: 26 mm (1 in)
  - Mean width: 10 mm (<0.5 in)
  - Mean area: 285 mm²
Penile Curvature: AUX-CC-801

Overall Percent Change From Baseline – Week 36

P=0.001
Peyronie’s Disease Bother Domain – AUX-CC-801

Overall Mean Score Change from Baseline – Week 36

P = 0.046

Change From Baseline

AA4500  N = 100
Placebo N = 34
Manual Modeling
Penile Curvature: AUX-CC-801

Modeling Percent Change From Baseline – Week 36

P = 0.001
Peyronie’s Disease Bother Domain – AUX-CC-801
With Modeling Mean Score Change from Baseline – Week 36

Change From Baseline

P = 0.004

AA4500 N = 100
Placebo N = 34
Penile Curvature $\geq 25\%$ Improvement at Week 36
Responder Analysis

Overall

Percent Of Subjects

AA4500 $N = 109$
Placebo $N = 36$
Safety: AUX-CC-801

Top Line Results

• Most common events
  – Injection site bruising (90%)
  – Injection site pain (55%)
  – Injection site edema (50%)

• Safety profile consistent with previous AA4500 studies
AUX-CC-803/804: Phase 3 Study Design

Prior to first dose subjects randomized by degree of penile curvature: 30° - 60° and 61° - 90°

Randomized into 2 treatment groups to receive in a 2:1 ratio either AA4500 or placebo and modeling

Dose of AA4500 0.58 mg in volume of .25 ml
2 doses per cycle given up to 4 cycles, each 6 weeks apart followed 24-72 hours later by penile modeling
The IMPRESS Study Design
Investigation for Maximal Peyronie’s Reduction Efficacy and Safety Studies

• Two double-blind, placebo-controlled phase III studies conducted at 64 sites in the U.S. and Australia
  - IMPRESS I: 32 Sites (27 in US, 5 in AUS)
  - IMPRESS II: 32 Sites (27 in US, 5 in AUS)
  - Subjects enrolled with penile curvature deformity from 20 to 90°
  - Randomized to receive up to 8 injections of XIAFLEX 0.58 mg or placebo in 2:1 ratio

• Co-primary endpoints
  - Percent improvement in penile curvature deformity
  - Improvement in Peyronie’s disease questionnaire (PDQ) bother domain score

• Safety assessments
IMPRESS Treatment Cycles

Induction of Erection
Penile Curvature Measurement
Primary Plaque Identified

XIAFLEX or Placebo Injection into Primary Plaque
24 to 72 hours
XIAFLEX or Placebo Injection into Primary Plaque
24 to 72 hours
Penile Plaque Modeling Procedure

Treatment Cycle
Subjects may receive up to four treatment cycles (up to 8 injections)
Each treatment cycle is separated by 6 weeks
**IMPRESS Study Subject Disposition**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IMPRESS I</th>
<th></th>
<th>IMPRESS II</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIAFLEX</td>
<td>Placebo</td>
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<td>Placebo</td>
</tr>
<tr>
<td><strong>ITT</strong></td>
<td>277 (100.0)</td>
<td>140 (100.0)</td>
<td>274 (100.0)</td>
<td>141 (100.0)</td>
</tr>
<tr>
<td><strong>Evaluable Penile Measurement</strong></td>
<td>275 (93.3)</td>
<td>139 (99.3)</td>
<td>270 (98.5)</td>
<td>139 (98.6)</td>
</tr>
<tr>
<td><strong>Evaluable PDQ</strong></td>
<td>199 (71.8)</td>
<td>104 (74.3)</td>
<td>204 (74.5)</td>
<td>107 (75.9)</td>
</tr>
<tr>
<td><strong>MITT</strong></td>
<td>199 (71.8)</td>
<td>104 (74.3)</td>
<td>202 (73.7)</td>
<td>107 (75.9)</td>
</tr>
<tr>
<td><strong>Completed</strong></td>
<td>241 (87.0)</td>
<td>124 (88.6)</td>
<td>236 (86.1)</td>
<td>127 (90.1)</td>
</tr>
</tbody>
</table>

* Requires a baseline and at least one post-injection evaluable PDQ
XIAFLEX Improved Penile Curvature Deformity over 52 Weeks

IMPRESS I
XIAFLEX: N=199, P=0.0005
Placebo: N=104

IMPRESS II
XIAFLEX: N=202, P=0.0059
Placebo: N=107
XIAFLEX 3-D Photographic Evaluation

Subject 1106-7852
Baseline curvature deformity – 48°
End of study curvature deformity – 28° (38% improvement)
XIAFLEX Improved PDQ Bother Domain Score over 52 Weeks

IMPRESS I
- XIAFLEX: 3.3 (44%)
- Placebo: 2.0 (27%)

IMPRESS II
- XIAFLEX: 2.4 (32.4%)
- Placebo: 1.6 (20.7%)

N=199 N=104 N=202 N=107

P=0.0451 P=0.0496

MIT Analysis. Bother Domain Score Range 0 to 16
Composite Responders Showed Improvement in Both Penile Curvature Deformity and Symptom Bother

Exploratory Composite Responder Definition:

- Improvement in penile curvature deformity ≥20%
- Improvement in the PDQ PD symptom bother domain score of ≥2, or a change from reporting no sexual activity at screening to reporting sexual activity

Hellstrom, WJG; AUA, 2014
Results: Percentage of Subjects With PD Who Were Composite Responders Using PD Bother Change ≥2 at Weeks 24 and 52

- Again, the group of men who received CCH treatment had a significantly greater percentage of composite responders compared with the placebo group at Week 24 and Week 52 (both P<0.0001)

Hellstrom, WJG; AUA, 2014
Conclusions

• A significantly greater percentage of CCH-treated PD subjects compared with placebo-treated subjects met the definition of composite responder
  • Composite responders showed improvement in both penile curvature deformity and PDQ PD symptom bother domain score

• The significantly greater percentage of composite responders in the CCH-treated subjects compared with placebo-treated subjects was shown at Week 24 and remained consistent at Week 52

• These findings support the clinical efficacy of CCH treatment compared with placebo for both the physical and psychosexual aspects of PD
Adverse Events
## Most Common Adverse Events ≥ 5%

<table>
<thead>
<tr>
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<td>N = 140 n (%)</td>
<td></td>
<td>N = 274 n (%)</td>
<td>N = 141 n (%)</td>
</tr>
<tr>
<td>Any non-serious AE</td>
<td>256 (92.4)</td>
<td>81 (57.9)</td>
<td>252 (92.0)</td>
<td>88 (62.4)</td>
</tr>
<tr>
<td>Penile hematoma</td>
<td>171 (61.7)</td>
<td>19 (13.6)</td>
<td>165 (60.2)</td>
<td>22 (15.6)</td>
</tr>
<tr>
<td>Penile Pain</td>
<td>119 (41.2)</td>
<td>11 (7.9)</td>
<td>96 (35.0)</td>
<td>8 (5.7)</td>
</tr>
<tr>
<td>Penile swelling</td>
<td>114 (41.2)</td>
<td>1 (0.7)</td>
<td>95 (34.7)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>70 (25.3)</td>
<td>5 (3.6)</td>
<td>41 (15.0)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Penile hemorrhage</td>
<td>60 (21.7)</td>
<td>14 (10.0)</td>
<td>43 (15.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Injection site hematoma</td>
<td>45 (16.2)</td>
<td>14 (10.0)</td>
<td>61 (22.3)</td>
<td>16 (11.3)</td>
</tr>
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ITT analysis/Preferred term listed
## Most Common Adverse Events ≥ 5%

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<td>n (%)</td>
<td>n (%)</td>
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</tr>
<tr>
<td>Penile edema</td>
<td>45 (16.2)</td>
<td>1 (0.7)</td>
<td>40 (14.6)</td>
<td>0 (0.0)</td>
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<tr>
<td>Injection site swelling</td>
<td>30 (10.8)</td>
<td>0 (0.0)</td>
<td>35 (12.8)</td>
<td>2 (1.4)</td>
<td></td>
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<tr>
<td>Contusion</td>
<td>28 (10.1)</td>
<td>0 (0.0)</td>
<td>27 (9.9)</td>
<td>1 (0.7)</td>
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<tr>
<td>Ecchymosis</td>
<td>26 (9.4)</td>
<td>0 (0.0)</td>
<td>12 (4.4)</td>
<td>0 (0.0)</td>
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<tr>
<td>Blood blister</td>
<td>9 (3.2)</td>
<td>0 (0.0)</td>
<td>17 (6.2)</td>
<td>0 (0.0)</td>
<td></td>
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<tr>
<td>Injection site hemorrhage</td>
<td>15 (5.4)</td>
<td>10 (7.1)</td>
<td>10 (3.6)</td>
<td>3 (2.1)</td>
<td></td>
</tr>
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*ITT analysis/Preferred term listed*
# Serious Adverse Events

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<td>Placebo</td>
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<tr>
<td><strong>N = 277</strong></td>
<td>27 (9.7)</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td><strong>n (%)</strong></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Treatment emergent SAE</strong></td>
<td>27 (9.7)</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td><strong>Treatment related SAE</strong></td>
<td>3 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>XIAFLEX Treatment Related SAEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hematoma</strong></td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Corporal Rupture (penile fracture)</strong></td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
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Successful Outcomes from IMPRESS Studies

- Peyronie’s disease is a common condition that can be both physically devastating and cause emotional anguish for men and their partners.

- XIAFLEX showed statistically significant improvements in both co-primary endpoints of the IMPRESS I and II Phase III studies:
  - Improvement [p-values of 0.0005 and 0.0059] in penile curvature deformity (physical)
  - Improvement [p-values of 0.0451 and 0.0496] in Peyronie’s disease bother (psychosocial)

- XIAFLEX is an effective FDA-approved biological therapy for the treatment of Peyronie’s disease.
Summary: What’s new in Peyronie’s Disease:
We now have an effective FDA-approved minimally invasive treatment available to treat our patients