ISSM Lecture:
Collagenase Clostridium Histolyticum (CCH) Injection Therapy: Update 2015

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History of ISSM

- Established in 1978 as the ISIR
- Initial focus was basic science, diagnosis and treatment of ED
- Now, as ISSM, has a broader focus to include all aspects of human sexuality
- >2500 members from all 5 continents and 90 nations
- Under the umbrella of ISSM, there are 7 affiliated professional societies
  - APSSM, ESSM, ISSWSH, MESSM, SASSM, SLAMS, SMSNA.
ISSM’s Regional Affiliated Societies

ISSWSH is an affiliated society to ISSM since January 1st, 2014. ISSWSH is an international society.
ISSM & RAS’s

- ISSM wants to deal with global issues and leave regional, national and local issues to regional, national and local societies.

- ISSM is the independent global partner for international activities on sexual medicine, both for physicians as well as for industry. International networks, global expert panels for standards and definitions, etc.
SAVE THE DATE

JUNE 19-21 2015

MELIA CASTILLA, MADRID, SPAIN

WWW.ICSM2015.ORG
JSM Family
ISSM’s new Video Journal of Prosthetic Urology (VJPU) is a peer-reviewed journal dedicated to publishing video content related to prosthetic urology in general and, in particular, related to sexual medicine.

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Benefits of ISSM Membership

- Journal of Sexual Medicine - 12 issues per year
- Sexual Medicine Reviews - 4 issues per year
- 80% Discount on the Author Publication Charges for the Open Access Journal "Sexual Medicine"
- Video Journal of Prosthetic Urology
- ISSM Members Discussion Forum
- Reduced Registration Fees for Meetings
- Weekly ISSM Update
- and more.....
Peyronie’s Disease: Psycho-sexual disorder

Background

• Scarring/plaque of the tunica albuginea with excessive abnormal collagen deposition

• Potential symptoms: 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%; average age of disease onset is 53 yrs

• Higher association with conditions such as diabetes, erectile dysfunction and others

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

1 Bella A, Peyronie’s Disease J Sex Med 2007;4:1527-1538
2 Nyberg L, J Urol. 128 48, 1982
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 (Mammalian vs. Clostridial)

Mammalian collagenases

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

Clostridial collagenase

- Fibrillar collagen types in vivo
- Cleaves multiple sites
- Relatively fast cleavage
- More complete degradation (degrades 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, M 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
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
Collagen Digestion in Peyronie’s Plaque

Gelbard et al. (1982), Urol Res 10: 135-140
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)

• FDA approved for Rx of Dupuytren’s contracture of hand (2009)
PD Treatment Options

• Spontaneous resolution
• Oral therapy - Vitamin E, PABA, Colchicine, Tamoxifen
• \textbf{Intralesional injection therapy}
  • Calcium channel blockers (Verapamil)
  • Interferon (IFN)
  • Collagenase (Xiaflex) – FDA approval Dec 6, 2013
• \textbf{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

CCH Mechanism of Action
CCH 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

**PDQ PD Symptom Bother Domain**

<table>
<thead>
<tr>
<th>PDQ PD Symptom Bother Domain Questions¹*</th>
</tr>
</thead>
<tbody>
<tr>
<td>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?</td>
</tr>
<tr>
<td>Q11. Thinking about the last time you looked at your erect penis, how bothered were you by the way your penis looked?</td>
</tr>
<tr>
<td>Q13. Thinking of the last time you had or tried to have vaginal intercourse, how bothered were you by your Peyronie’s disease?</td>
</tr>
<tr>
<td>Q15. How bothered are you with having vaginal intercourse less often?</td>
</tr>
</tbody>
</table>

*Q12 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
Penile Curvature: AUX-CC-801

Overall Percent Change From Baseline – Week 36

Percent Change From Baseline

P=0.001

-29.7
-11.0

AA4500
Placebo
Peyronie’s Disease Bother Domain – AUX-CC-801

Overall Mean Score Change from Baseline – Week 36

Change From Baseline

P = 0.046

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

Modeling Percent Change From Baseline – Week 36

P=0.001

Percent Change From Baseline

-32.4

AA4500

Placebo
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
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
Subjects may receive up to four treatment cycles (up to 8 injections)

Each treatment cycle is separated by 6 weeks

Induction of Erection
Penile Curvature Measurement
Primary Plaque Identified

24 to 72 hours

XIAFLEX or Placebo Injection into Primary Plaque

24 to 72 hours

XIAFLEX or Placebo Injection into Primary Plaque

Penile Plaque Modeling Procedure
## IMPRESS Study Subject Disposition

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IMPRESS I</th>
<th>IMPRESS II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIAFLEX</td>
<td>Placebo</td>
</tr>
<tr>
<td>ITT N (%)</td>
<td>277 (100.0)</td>
<td>140 (100.0)</td>
</tr>
<tr>
<td>Evaluable Penile Measurement</td>
<td>275 (93.3)</td>
<td>139 (99.3)</td>
</tr>
<tr>
<td>Evaluable PDQ*</td>
<td>199 (71.8)</td>
<td>104 (74.3)</td>
</tr>
<tr>
<td>MITT</td>
<td>199 (71.8)</td>
<td>104 (74.3)</td>
</tr>
<tr>
<td>Completed</td>
<td>241 (87.0)</td>
<td>124 (88.6)</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

MIT Analysis
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

IMPRESS II

PDQ Bother Scale

MIT Analysis. Bother Domain Score Range 0 to 16
Adverse Events
Most Common Adverse Events ≥ 5%

<table>
<thead>
<tr>
<th></th>
<th>IMPRESS I</th>
<th></th>
<th>IMPRESS II</th>
<th></th>
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<tr>
<td></td>
<td>XIAFLEX</td>
<td>Placebo</td>
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<td>Placebo</td>
</tr>
<tr>
<td>Penile edema</td>
<td>N = 277</td>
<td>45 (16.2)</td>
<td>N = 274</td>
<td>40 (14.6)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>1 (0.7)</td>
<td>n (%)</td>
<td>0 (0.0)</td>
</tr>
<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>
</tr>
<tr>
<td>Contusion</td>
<td>28 (10.1)</td>
<td>0 (0.0)</td>
<td>27 (9.9)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>26 (9.4)</td>
<td>0 (0.0)</td>
<td>12 (4.4)</td>
<td>0 (0.0)</td>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

ITT analysis/Preferred term listed
## Serious Adverse Events

### IMPRESS I

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<tbody>
<tr>
<td>n (%)</td>
<td>N = 277</td>
<td>N = 140</td>
</tr>
<tr>
<td>Treatment emergent SAE</td>
<td>27 (9.7)</td>
<td>7 (5.0)</td>
</tr>
<tr>
<td>Treatment related SAE</td>
<td>3 (1.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

### IMPRESS II

<table>
<thead>
<tr>
<th></th>
<th>XIAFLEX</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>N = 274</td>
<td>N = 141</td>
</tr>
<tr>
<td>Treatment emergent SAE</td>
<td>12 (4.4)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Treatment related SAE</td>
<td>3 (1.1)</td>
<td>0 (0.0)</td>
</tr>
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### XIAFLEX Treatment Related SAEs

<table>
<thead>
<tr>
<th></th>
<th>XIAFLEX</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma</td>
<td>2 (0.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Corporal Rupture</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

ITT analysis/Preferred term listed
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.