Intralesional collagenase in the treatment of Peyronie’s disease

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Abstract: The objective of intralesional pharmacotherapy in the treatment of Peyronie’s disease is to deliver large doses of pharmacologic agents that can have a local effect on wound remodeling, with minimal side effects. Guidelines for the treatment of peyronie’s disease published in the Journal of Sexual Medicine and the European Association of Urology offer no grade A evidence of efficacy with multiple agents such as steroids, verapamil and interferon. Intralesional collagenase is the first drug to be approved by the United States Food and Drug Administration for the treatment of Peyronie’s disease. This is based on grade A evidence. The purpose of this update is to review the literature and current data on intralesional collagenase in the treatment of Peyronie’s disease.

Keywords: Peyronie’s disease, collagenase, intralesional

Introduction
Peyronie’s disease is thought to occur from a combination of trauma and a genetic predisposition to abnormal wound healing. This event starts a cascade of inflammatory responses, including release of transforming growth factor β, development of reactive oxygen species, excess collagen and fibrin deposition that may result in penile scarring and plaque formation. Secondary sequelae such as penile shortening, curvature and disfigurement may occur. This can be physically and psychologically devastating. Quality of life may be affected and may result in depression, lower self esteem and fear of sexual activity [Nelson et al. 2008]. At the present time, there are no European Medical Association approved treatments for Peyronie’s disease. However, intralesional collagenase has recently been FDA approved in the United States. The purpose of this update is to review the literature and current data on intralesional collagenase in the treatment of Peyronie’s disease.

The objective of intralesional pharmacotherapy in the treatment of Peyronie’s disease is to deliver large doses of pharmacologic agents that can have a local effect on wound remodeling, with minimal side effects. Multiple agents have been tested, including steroids, verapamil, collagenase and interferon, among others [Szobota and Honig, 2008]. These treatments are well tolerated by patients and dropout rates are quite low. Despite an unclear therapeutic benefit, off-label intralesional injection therapy has become the mainstay of treatment for Peyronie’s disease. When evaluating benefit, attention to specific endpoints, that is, curvature, plaque size, erectile function, and most recently, patient bother, need to be scrutinized in a critical, evidence-based fashion.

Prior data and guidelines
The guidelines for the treatment of Peyronie’s disease published in the Journal of Sexual Medicine 2010 (JSM) and by the European Association of Urology (EAU) evaluate evidence-based therapy for this disease [Hatzimouratidis et al. 2012; Ralph et al. 2010]. The JSM guidelines, based on grade B evidence, suggest that there is no benefit with respect to deformity reduction with any oral therapy, including vitamin E, potassium aminobenzoate, colchicine, tamoxifen and carnitine. Subsequent recommendations in the guidelines regarding nonsurgical treatment of Peyronie’s disease, based on grade C evidence, state that ‘non surgical treatment has limited evidence of benefit, but multiple reports of deformity stabilization or reduction makes it reasonable to offer EMDA (electromotive drug
administration) and/or intrallesional injection of verapamil, interferon and/or traction therapy' [Ralph et al. 2010]. Intrallesional verapamil is an option based on grade C evidence. Regarding intrallesional interferon, one double-blind, placebo-controlled trial (grade B evidence) suggests an outcome benefit. The EAU guidelines state that ‘intrallesional treatment with verapamil (grade C evidence) and collagenase (grade C evidence) and interferon (grade B evidence) may improve penile curvature and plaque size’ [Hatzimouratidis et al. 2012]. Recently, renewed interest in intrallesional collagenase Clostridium histolyticum (CCH) has spawned some interesting well-performed studies.

**Background**

Collagenases are enzymes capable of degrading interstitial collagens (i.e. type II collagen). CCH is a mixture of two collagenases: AUX-1 and AUX-2. Collagenase has been utilized in the treatment of chronic dermal ulcers and severely burned tissues, and tested in the treatment of herniated lumbar disks [Kastrip, 2005; Bromley, 1985; Brown and Tompkins, 1986]. It is currently approved by the Food and Drug Administration (FDA) and European Medical Association (EMA) for use in men with a palpable cord due to Dupuytren’s contracture [Hurst et al. 2009]. A randomized, double-blind, placebo-controlled, multicenter trial using CCH injected into a Dupuytren’s contracture followed by a finger extension procedure showed a statistically significant improvement in range of motion and contracture size, thus meeting both primary and secondary endpoints. With exciting results in Dupuytren’s contracture, the use of CCH was revisited in the treatment of Peyronie’s disease.

**Historical data**

From a historical perspective, Gelbard and colleagues performed an in vitro pilot study in which collagenase was injected into removed Peyronie’s plaques [Gelbard et al. 1982]. Initial work by the group examined the effect of collagenases in vitro on human pericardium, corpus cavernosum, tunica albuginea and Peyronie’s plaques. A decrease in plaque size and dispersal of collagen bundles was noted.

Armed with these laboratory data, Gelbard and colleagues performed a phase I pilot clinical study using injected intrallesional collagenases in 31 men with Peyronie’s disease [Gelbard et al. 1985]. The mean age of participants was 55.5 and they had a history of Peyronie’s disease with a mean interval disease onset of 22.2 months and a mean curvature of 42°. Intrallesional injections of collagenase were given daily for 3 days. Six patients were given collagenase alone, while seven patients received topical β-aminopropionitrile fumarate (an antifibrotic medication) and 17 patients received oral β-aminopropionitrile fumarate. Four weeks later, follow up showed objective improvement in curvature in 65% of patients, elimination of pain in 90%, and reduction or disappearance of plaques in nearly 70%. Injections were well tolerated, with only local pain and ecchymosis. There was no breakdown regarding the effects of the antifibrotic medications. One patient had a tunical rupture during intercourse 2 weeks after treatment [Gelbard et al. 1985; Glina et al. 2007].

In a follow-up phase I study [Gelbard et al. 1993] evaluated 49 men in a single-center, randomized, double-blind, placebo-controlled trial with intrallesional injection of purified clostridial collagenases versus placebo.

The patients were divided into three groups based on degree of penile curvature and plaque size (<30° and <2 cm, 30–60° and 2–4 cm, or >60° and >4 cm). Patients received a cumulative volume of 6000, 10,000 and 14,000 U of purified clostridial collagenases respectively. After 3 months, if patients received placebo, they were enrolled in an open-label collagenase arm. Penile curvature was measured by photography with erections obtained using a vacuum erection device. Response rates of drug versus placebo (in curvature and plaque size) at a short 3-month follow up were 100% versus 25% (group 1), 36% versus 0% (group 2) and 13% versus 0% (group 3). The subsequent open-label study of patients receiving placebo showed a 56% improvement with collagenase. Due to insufficient study power, statistical significance was seen only in the 30–60° group, although there was overall statistically significant improvement in the total group. Most side effects were local, with one penile ‘tear’ that was treated conservatively.

Fifteen years later, Jordan reported preliminary data on a 9-month, open-label, single-center study with collagenase in a heterogeneous population of patients with Peyronie’s disease [Jordan, 2008]. Three injections were given over a 10-day period with a similar regimen of injections at 3 months (n = 25). Injections had a lower volume...
and higher total collagenase concentration than the 1993 Gelbard study. Primary endpoints were changes from baseline in curvature and plaque size. Clinical success was defined as a reduction of over 25% in angle of deviation or a 2.5 cm reduction in plaque size. There was no statistically significant difference in success at 3, 6 or 9 months based on these criteria. However, regarding evaluation of mean angle of deviation, there was statistically significant improvement in mean angle of deviation from approximately 50° to less than 15°. In follow-up studies on mean angle of deviation at 9 months, 72% (18/25) maintained this early success if given repeat injections at 3 months. However, at 9-month follow up, slight regression was seen (back up to 28°). The author states that this occurred due to the lack of follow up with successful patients and at 9 months these data lacked statistical significance. The mean change from baseline in plaque width was significant at 3, 6 and 9 months. The mean change from baseline in plaque length was significant at 3 and 6 months only. There was improvement in sexual quality of life based on a nonvalidated questionnaire. There were no significant adverse effects except local issues, such as pain, contusions and ecchymosis, which resolved spontaneously.

Recent data

With the new results in the Jordan open-label study in 2008, a phase Ib study of the clinical efficacy and safety of intralvesional CCH in Peyronie’s disease was initiated [Gelbard et al. 2012]. Primary endpoints were percentage improvement from baseline in penile curvature deformity and the change from baseline in Peyronie’s Disease Symptom Bother Domain score assessed using the Peyronie’s Disease Questionnaire (PDQ), both compared with placebo at 36 weeks. The PDQ is a new questionnaire that was utilized initially in this phase II study and then improved, validated and utilized in subsequent phase III studies [Hellstrom et al. 2013]. The PDQ assesses treatment-related improvements in Peyronie’s disease symptoms and is composed of three essential subscale domains: psychological and physical symptoms (six questions), penile pain (three questions) and symptom bother (four scored questions and two yes/no questions). Each domain is intended to be an independent measure, not summed for a ‘total’ instrument score. This subjective evaluation was utilized as a primary endpoint in this study.

Inclusion criteria for the phase II study were patients in a stable heterosexual relationship, diagnosis of Peyronie’s disease for at least 6 months and penile curvature in any direction except ventral. Patient curvature was required to be between 30 and 90° without a calcified plaque, no erectile dysfunction (ED) or ED that responded to phosphodiesterase type 5 (PDE5) inhibitors or intracavernosal injection. Exclusion criteria included calcified plaque by radiography,
prior surgery or recent treatment with oral or other intralesional therapy, or an isolated hourglass deformity without curvature.

A total of 147 patients were randomized into four groups to receive CCH or placebo (3:1), with or without penile modeling (Figure 1). Patient demographics and histories are reported in Table 1 and 2. Treatment cycles included two injections within 48 h followed by penile modeling by a physician within 72 h and subsequent ‘home’ modeling three times daily. The penile modeling included gradual, gentle stretching of the flaccid penis in the opposite direction of the curvature. This was then held in position for 30 s and repeated three times. This cycle of treatment was repeated every 6 weeks for up to three cycles. Procedures were terminated if there was improvement to less than a 15° angle. The results are shown in Figure 2. There was statistically significant improvement in penile curvature in the treated group versus the placebo group (29% versus 11%, p = 0.001). In the modeling group, 32% improvement in curvature was seen in the CCH group versus 2.5% worsening in the placebo group. Regarding patient-reported outcomes, there was also a statistically significant difference between CCH versus placebo in improvement in symptom bother (−2.6 versus −0.07, p < 0.004). This difference was not seen in the group without modeling, suggesting an additive effect of modeling to the activity of the collagenase. There were no major adverse events, although there was a significant amount of bruising, edema and pain [Gelbard et al. 2012].

Based on these phase IIb data, two separate phase III multicenter, randomized, double-blind, placebo-controlled trials were initiated in the United States (IMPRESS 1) and Australia (IMPRESS 2) [Gelbard et al. 2013]. Primary endpoints in these studies were percentage improvement from baseline in penile curvature deformity and the change from baseline in the PDQ Symptom Bother Domain score, both compared with placebo. The data presented below are based on a combination of the two separate studies.

### Table 1. Intention-to-treat population demographic and baseline characteristics.

<table>
<thead>
<tr>
<th>Modeling</th>
<th>Placebo</th>
<th>No modeling</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients (n)</strong></td>
<td>54</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td><strong>Age, mean ± SD (range)</strong></td>
<td>57.4 ± 7.4 (36–72)</td>
<td>56.6 ± 6.4 (38–68)</td>
<td>56.6 ± 8.2 (28–71)</td>
</tr>
<tr>
<td><strong>Age, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 45</td>
<td>3 (5.6)</td>
<td>1 (5.0)</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td>45–64</td>
<td>42 (77.8)</td>
<td>17 (85.0)</td>
<td>45 [78.9]</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>9 [16.7]</td>
<td>2 [10.0]</td>
<td>7 [12.3]</td>
</tr>
<tr>
<td><strong>Degrees penile curvature, mean ± SD (range)</strong></td>
<td>54.7 ± 15.2 (33–89)</td>
<td>51.9 ± 15.9 (30–90)</td>
<td>54.1 ± 15.1 (30–90)</td>
</tr>
<tr>
<td><strong>Weight (kg), mean ± SD</strong></td>
<td>85.4 ± 10.4</td>
<td>84.9 ± 12.2</td>
<td>86.5 ± 10.4</td>
</tr>
<tr>
<td><strong>Height (cm), mean ± SD</strong></td>
<td>178.6 ± 7.8</td>
<td>175.3 ± 7.6</td>
<td>179.1 ± 6.8</td>
</tr>
<tr>
<td><strong>Hispanic/Latino ethnicity, n (%)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>1 (5.0)</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td>No</td>
<td>54 (100.0)</td>
<td>19 (95.0)</td>
<td>55 (96.5)</td>
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<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3 (5.6)</td>
<td>0</td>
<td>3 (5.3)</td>
</tr>
<tr>
<td>White</td>
<td>51 (94.4)</td>
<td>20 (100.0)</td>
<td>54 (94.7)</td>
</tr>
<tr>
<td><strong>Alcohol use, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6 (11.1)</td>
<td>5 (25.0)</td>
<td>13 (22.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>46 (85.2)</td>
<td>12 (60.0)</td>
<td>39 (68.4)</td>
</tr>
<tr>
<td>Previously</td>
<td>2 (3.7)</td>
<td>3 (15.0)</td>
<td>5 (8.8)</td>
</tr>
<tr>
<td><strong>Tobacco use, n (%)</strong></td>
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<tr>
<td>No</td>
<td>28 (51.9)</td>
<td>10 (50.0)</td>
<td>30 (52.6)</td>
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<tr>
<td>Yes</td>
<td>5 (9.3)</td>
<td>3 (15.0)</td>
<td>9 (15.8)</td>
</tr>
<tr>
<td>Previously</td>
<td>21 (38.9)</td>
<td>7 (35.0)</td>
<td>18 (31.6)</td>
</tr>
</tbody>
</table>

CCH, collagenase Clostridium histolyticum. (with permission)
A total of 836 patients were initially randomized and 612 patients (73%) completed the study. Inclusion criteria were patients in a stable heterosexual relationship, diagnosis of Peyronie’s disease for at least 12 months (as opposed to 6 months in the phase IIb study) and penile curvature in any direction except ventral. Patient curvature was required to be between 30° and 90° without a calcified plaque, no ED or ED that responded to PDE5 inhibitors or intracavernosal injection, and no prior Peyronie’s surgery.

Treatment cycles included two injections within 48 h followed by penile modeling by a physician within 72 h and ‘home’ modeling three times daily. Patients were asked to ‘gently attempt straightening the penis without pain during spontaneous erections’. In the phase III study, all patients underwent penile modeling by a physician as described in the phase II trial. In addition to the phase II modeling protocol, patients were asked to straighten the flaccid penis in the opposite direction of curvature three times per day for 6 weeks. Patients were also asked to ‘gently attempt straightening the penis without pain during spontaneous erections’. This cycle was repeated every 6 weeks for up to four cycles (three cycles in phase IIb). Procedures were terminated if there was improvement to less than a 15° angle.

As stated earlier, primary endpoints were percentage improvement from baseline in penile curvature deformity at 52 weeks; and change from baseline in Peyronie’s disease symptoms in PDQ questionnaire. The change in total score for the Peyronie’s disease symptom domain (four questions, total score range 0–16) was assessed using the PDQ. The PDQ was validated for the phase III trial [Hellstrom et al. 2013].

Secondary endpoints included proportion of treatment responders using the global assessment...
of the PDQ; change in International Index of Erectile Function; percentage of responders with an improvement of more than 20% in penile curvature and an improvement in PDQ (global responders); change in penile plaque consistency; penile length; and penile pain domain.

There was a statistically significant improvement in both mean penile curvature deformity change measured in the erect penis using intracavernosal injection (34% versus 17%, p < 0.0001) and mean change in PDQ Symptom Bother domain (2.8 versus 1.8, p < 0.003) in the CCH group versus the placebo group.

Regarding secondary endpoints, in the combined study meta-analysis all secondary endpoints except penile length and penile pain were met.

In this author’s opinion, the most important endpoint, global responders (i.e. those that had at least a 20% improvement in curvature and improvement in PDQ), was statistically significant in the individual studies and in the meta-analysis combination studies (IMPRESS, 1 66% versus 29%, p < 0.0001; IMPRESS 2, 55.4% versus 29.9%, p < 0.0001; combined analysis, 60.8% versus 29.5%, p < 0.0001).

Safety

Safety and tolerability were analyzed as well. There was a significant amount of relatively minor local adverse reactions in the collagenase group versus placebo, such as penile ecchymosis (80% versus 26%), swelling (55% versus 3%) and pain (45% versus 9%). In addition, there were six significant adverse events in the collagenase group: three corporal ruptures and three penile hematomas. The three corporal ruptures and one hematoma were successfully surgically repaired; one hematoma resolved spontaneously and one resolved with aspiration. There were no significant adverse effects in the placebo group. This adverse event profile was very similar to that seen with treatment of Dupuytren’s contracture.

Follow up studies

Certain populations were excluded that might benefit from treatment, i.e. patients with calcified plaques and ventral curvature. In addition, it is unclear whether penile modeling had a significant effect on the overall effects of treatment as placebo groups did see an improvement in both curvature and PDQ scores. These subjective placebo effects, however, are very similar to those seen in other sexually related studies with PDE inhibitors, such as sildenafil, vardenafil and tadalafil.

Intralesional collagenase is the first U.S. FDA approved drug for the treatment of Peyronie’s disease. Intralesional collagenase is also currently being tested in the treatment of frozen shoulder, lipomas and cellulite. Further studies and clinical experience will determine the role of intralesional collagenase in the treatment of Peyronie’s disease.

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Conflict of interest statement

The author is on the Auxilium advisory board and participated in the clinical trials on intralesional collagenase.

References


