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Intralesional collagenase *Clostridium histolyticum* in the management of Peyronie's disease: current best practice

Daniel J. Cwikla and Faysal A. Yafi

Abstract: The use of *Clostridium histolyticum* collagenase (CCH) has become increasingly widespread for the treatment of Peyronie's disease (PD) in recent years. Numerous trials have confirmed both its safety and efficacy in appropriately selected patients with this condition. The purpose of this review is to examine pivotal trials demonstrating the efficacy of CCH, revisit viable candidates for treatment with intralesional injection therapy, and provide a summary of injection technique and appropriate management of patients receiving this treatment at the time of therapy and in follow up.

Keywords: *Clostridium histolyticum* collagenase, intralesional injection therapy, Peyronie's disease

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Introduction

Peyronie's disease (PD) is a localized connective tissue disorder of the penis marked by focal fibrosis leading to penile deformity, sexual dysfunction, emotional distress, and pain.^{1–11} Prevalence of the condition ranges from 3% to 9% with most men presenting between the ages of 52 and 57.^{6,7} PD is thought to be due to abnormal wound healing and aberrant collagen deposition leading to the formation of fibro-collagenous plaques within the tunica albuginea.^{12–15} The plaques themselves do not undergo a normal process of remodeling, resulting in penile curvature and deformity which often persists or progresses despite resolution of physical discomfort.¹⁶ As a result, many patients with PD continue to suffer from both psychological distress and negative effects on their emotional and sexual relationships with their partners.^{9–11} These can be profound, with patients noting numerous issues impacting their quality of life including performance anxiety, concern regarding physical appearance, painful intercourse, loss of sexual confidence, concerns regarding partner satisfaction, and concerns regarding attractiveness.^{10,17} In a single study in 2008, 54% of men experienced relationship problems and 81% emotional distress attributable to PD.¹⁰

Standard of care for treatment of PD has long been surgical. This can be effective but may also have undesirable side effects, including penile shortening, glans numbness, neurovascular injury, and erectile dysfunction.^{18,19} Other treatment options have been explored including oral therapeutics, extracorporeal shockwave therapy, and intralesional injection therapy (ILI). Among these, ILI has proved the most promising and is the only alternate treatment currently recommended by the American Urological Association (AUA).²⁰ Collagenase *Clostridium histolyticum* (CCH), marketed as Xiaflex (Endo Pharmaceuticals, Malvern, PA, USA) is the sole form of ILI currently approved by the US Food and Drug Administration (FDA), carrying with it a level B recommendation according to the 2015 AUA Guideline on PD.²¹ This article provides an overview of the literature regarding the use of CCH and the current best practice in its treatment of men with PD.

Collagenase *Clostridium histolyticum*

Pathophysiology

CCH is a purified mixture of two clostridial collagenases which work in conjunction to degrade the predominant forms of collagen found in PD

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plaques.²² Initially isolated in the mid 1950s, CCH was first described showing effectiveness in PD by Gelbard and colleagues in 1982.^{22–25} CCH consists of two isoforms of collagenase, AUX-I and AUX-II, contained in a phosphate buffer.²⁶ These enzymes manifest their effects through hydrolysis of types I and III collagen fibers (found in bone, connective tissue, scar, and PD plaques) while sparing collagen type IV (found in vascular and nervous tissues).^{22–26} *Ex vivo* studies have confirmed that each form of collagenase cleaves collagen fibers at a different site, leading to the synergistic effect of CCH.²⁵

Clinical trials

Investigations into the use of CCH for the treatment of PD have been carried out for over 30 years, with the earliest studies published by Gelbard and colleagues in 1985.²⁴ In this initial phase I trial, 31 patients received ILI with varying doses of CCH. Six patients received injections 3 days consecutively with doses ranging from 270 to 1595 units to establish dosage. The remaining 25 patients received daily injections of ILI for three consecutive days with dosages ranging from 1739 to 4850 units. Patients were seen after 4 weeks with evaluations of several measures, including penile curvature, plaque size, and penile pain. Of the 31 patients, 20 (65%) showed objective improvement in penile curvature, with 16 having improvement ranging from 20% to 100% and the remaining four with virtual disappearance of their plaques. Resolution of symptoms was noted in 13 of the 14 patients with complaints of pretreatment painful erections. The authors noted a single small corporal rupture at the injection site in one patient during the course of the study.

Gelbard and colleagues then completed the first placebo-controlled, double-blind, randomized study to assess the efficacy of CCH in 1993.²⁷ Forty-nine patients were enrolled and stratified into three groups based on their degree of penile curvature and size of plaque. Men in each group were then randomized to receive either CCH injections with dosages based on their severity of PD manifestations (more severe curvature or plaque size received higher dosages) or placebo. Overall, more patients receiving CCH did demonstrate a positive overall response which was statistically significant, with 8 of 22 (36.3%) in the CCH group as opposed to 1 of 27 (3.7%) in the placebo group ($p = 0.007$).

No studies regarding the efficacy or safety of CCH were undertaken for nearly 15 years until a new study was conducted by Jordan and colleagues in 2008.²⁸ Prospective, single-center, and nonplacebo controlled, this trial enrolled 25 patients aged 21–75 with well defined PD plaques for treatment. These patients underwent three intralesional injections of 10,000 U (0.58 mg) CCH over the course of 7–10 days with a follow-up treatment of three injections after 3 months. Primary endpoints were defined by changes from baseline in terms of penile curvature and plaque size. Overall, of the 19 patients who completed the study, 53% experienced a positive response for penile curvature and 94% for plaque size.

This was followed by a phase IIb randomized, double-blind, placebo-controlled study of CCH in patients with PD from 12 American sites in which 147 patients were enrolled and subsequently stratified according to their degree of curvature: less than 60° versus more than 60°.²⁹ These patients were then randomized to receive either CCH or placebo at a 3:1 ratio respectively as well as manual modeling at a 1:1 ratio. Patients received up to three cycles of two injections each of 10,000 U (0.58 mg) CCH. Injections themselves were spaced 24–72 h apart and were made at the point of maximum curvature of the plaque. Those patients randomized to manual modeling underwent gradual stretching of the penis for 30 s in the direction opposite 24–72 h after the second injection of each cycle. This was completed three times.

A statistically significant reduction in curvature, 29.7% ($-16.3^\circ \pm 14.6^\circ$) compared with 11.0% ($-5.4^\circ \pm 13.8^\circ$; $p < 0.001$), was demonstrated in patients receiving CCH rather than placebo. Patients who underwent manual modeling showed a greater response to treatment, with an overall improvement of 32.4% in penile curvature ($-17.5^\circ \pm 15.3^\circ$), as opposed to a 3.0% change in curvature in the placebo group ($0.6^\circ \pm 13.2^\circ$; $p < 0.001$).

IMPRESS trials

Two of the most pivotal trials regarding the use of CCH, IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II examined the clinical efficacy and safety of ILI with CCH for the treatment of subjects with PD.³⁰ Published in 2013, these studies were identical, prospective, multi-institutional, randomized,

Table 1. Inclusion and exclusion criteria for selection of study population in IMPRESS I and II.

<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Healthy men age 18 or older in a stable relationship with a female partner/spouse (for at least 3 months) and willing to have vaginal intercourse with that female partner/spouse • Diagnosis of PD for at least 12 months with evidence of stable disease as determined by the investigator • Penile curvature of at least 30° in the dorsal, lateral, or dorsal/lateral plane (must have been possible to delineate the single plane of maximal curvature for evaluation) • Signed informed IRB-approved consent agreement; signed authorization form to allow disclosure of protected health information • Ability to read, complete, and understand the various rating instruments in English <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Penile curvature of <30° or >90° • Any conditions affecting the penis, such as chordee in the presence or absence of hypospadias; thrombosis of the dorsal penile artery; infiltration by a benign or malignant mass or an infectious agent; ventral curvature from any cause; presence of an active sexually transmitted disease; known active hepatitis B or C; known immune deficiency disease (including HIV) • Failure to achieve a sufficient erection (after prostaglandin E or Trimix administration), in the opinion of the investigator, to accurately measure the penile deformity • Calcified plaque as evident by appropriate radiographic evaluation, penile X-ray, or penile ultrasound (noncontiguous stippling allowed) that would prevent proper injection of study medication • Isolated hourglass deformity of the penis without curvature • Plaque causing curvature of the penis located proximal to the base of the penis (injection of the local anesthetic would interfere with the injection of CCH into the plaque) • Treatment or plans to undergo treatment for PD, including but not limited to any previous surgery, oral/topical agents within 3 months, intralesional medical therapies within 3 months, extracorporeal shock wave therapy within 6 months, or use of mechanical devices within 2 weeks before the start of the study • Use of or plans to use a mechanical device to induce a passive erection within 2 weeks before the start of the study • ED that was unresponsive to PDE5 inhibitors • Compromised penile hemodynamics (determined by penile duplex Doppler ultrasound) found at screening that are determined by the investigator to be clinically significant • Uncontrolled hypertension (determined by the investigator), known recent history of stroke, bleeding, or other significant medical condition, which in the investigator's opinion would make the subject unsuitable for enrollment • Received an investigational drug or treatment (including CCH) within 30 days before start of the study • Allergy to collagenase or other medication required by the protocol • Received anticoagulant medication (except for ≤165 mg aspirin daily or ≤800 mg of over-the-counter NSAIDs daily) during the 7 days before each dose of study drug • At any time, received CCH for the treatment of PD <p>CCH, collagenase <i>Clostridium histolyticum</i>; ED, erectile dysfunction; HIV, human immunodeficiency virus; IMPRESS, Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies; NSAID, nonsteroidal anti-inflammatory drug; PD, Peyronie's disease; PDE5, phosphodiesterase type 5.</p>

double-blinded placebo-controlled phase III studies which enrolled a total of 832 subjects (417 and 415 subjects, respectively). Strict inclusion and exclusion criteria were used and are included in Table 1. Men were stratified according to the severity of curvature (31°–60° versus 61°–90°) and subsequently randomized to receive either injections of CCH or placebo at a ratio of 2:1 favoring the former.

Study participants underwent up to a total of four treatment cycles, each cycle consisting of up to two injections of 10,000 U (0.58 mg) of CCH or placebo spaced 24–72 h apart, with cycles

themselves spaced 6 weeks apart. Injections into the plaque were made at the point of maximum curvature and following the second injection in each cycle, manual modeling was performed by the investigator 24–72 h later. Manual modeling consisted of the application of firm, steady pressure in order to elongate and stretch the penis by the clinician for 30 s a total of three times. Patients were also instructed to perform identical manual modeling techniques themselves three times daily during the intervening 6 weeks between cycles. Further cycles were not carried out if penile curvature was reduced to less than 15° after the first cycle.

Table 2. Combined IMPRESS trial analysis and outcomes.

Primary endpoints			
	CCH	Placebo	<i>p</i> value
Percent change in degree of curvature			
Number of subjects	401	211	
Baseline (°)	50.1 ± 14.4 (48.0)	49.3 ± 14.0/46.0	
Week 52 (°)	33.1 ± 16.8/32.0	40.0 ± 16.2	
% change	-34.0/-34.8	-18.2/-18.2	< 0.0001
Mean PDQ bother score			
Baseline	7.5 ± 3.5	7.8 ± 3.7	
Week 52	4.6 ± 3.8	6.0 ± 4.0	
Change	-2.8 ± 3.8	-1.8 ± 3.5	0.0037
Secondary endpoints			
% Global responders	60.8	29.5	<0.0001
Decrease in PD symptoms	-2.9 ± 5.0	-1.3 ± 4.6	0.0021
Change in IIEF	1.0 ± 2.4	0.4 ± 2.4	0.0189
% Composite responders	46.6	28.8	<0.0001
Change plaque consistency	-0.8 ± 1.0	-0.5 ± 1.0	0.0133
Change in penile length (cm)	0.4 ± 1.3	0.2 ± 1.3	0.0408
Change in penile pain	-4.4 ± 5.6	-4.3 ± 4.8	0.9672

CCH, collagenase *Clostridium histolyticum*; IIEF, International Index of Erectile Function; IMPRESS, Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies; PD, Peyronie's Disease; PDQ, Peyronie's Disease Questionnaire.

Coprimary efficacy endpoints were set forth for the study, namely percent change in curvature from baseline and improvement in bother symptoms as assessed by the Peyronie's Disease Questionnaire (PDQ). Percent change in curvature was determined based on change in degree of curvature from the outset of the study to week 52 as measured by a standardized goniometer and then compared with placebo. Improvement in bother symptoms was assessed from four questions on the standardized 16-question PDQ, a validated and highly sensitive questionnaire developed for phase III use with this study and designed to assess PD symptoms in three major domains: psychological and physical symptoms, pain, and bother-type symptoms (Table 2).

Inclusion criteria

Highly selective inclusion and exclusion criteria were utilized in the design of the IMPRESS trials,

allowing for highly standardized results but also narrowing the applicability of the study. The authors themselves noted at the time of publication that this was a principal weakness of their study, with the population consisting predominantly of white men with mature plaques and moderate curvature. Patients were to have stable, noncalcified plaques with only dorsal or lateral curvature. Multiple forms of atypical PD were excluded, including ventral curvature due to concern regarding injuring the urethra, hourglass deformity, and active phase PD. These are summarized in Table 1.

Outcomes

Men treated with CCH showed a mean 34.0% improvement in penile curvature, representing a mean ± SD $-17.0^\circ \pm 14.8^\circ$ change per subject, compared with a mean 18.2% improvement in placebo-treated men, representing a mean $-9.3^\circ \pm$

13.6° change per subject ($p < 0.0001$). Both the percent change in curvature as well as the absolute change in degree of curvature were significantly greater in the CCH group ($p < 0.001$). Mean change in PDQ scores was significantly greater in the CCH groups *versus* placebo as well (-2.8 ± 3.8 *versus* -1.8 ± 3.5 ; $p = 0.0037$). Aside from changes in penile length and penile pain, all secondary endpoints were also statistically significant in favor of CCH (Table 2). Table 3 summarizes all studies major CCH studies for the management of PD.

Patient satisfaction

PD is a condition which manifests not only with physical deformity but with significant psychological and emotional consequences for patients and their partners.^{10,17} To date, multiple investigations have evaluated ILI with CCH in order to verify its safety, efficacy, and durability in the treatment of the physical aspects of PD. However, despite these studies showing clinical effectiveness, there is a relative paucity of data regarding changes in patients' quality of life, psychological impact, change in relationships with partners, and overall satisfaction with treatment by way of ILI.

During the course of the IMPRESS trials, two separate measures for subjective improvements were used: PDQ and Global Assessment of PD (GAPD). As described previously, the PDQ is a 16-question survey used to determine patient's psychological and physical symptoms, pain, and bother, three major subjective domains associated with PD. GAPD is a second rating scale used to describe change in overall quality of life, effect of PD, and change in symptoms following the initiation of CCH therapy. Scores are placed on a scale of -3 to 3 , with a score of -3 denoting a patient who feels he is much worse since therapy and a score of 3 indicating a patient who believes he is much better. Changes in each of these scores were analyzed after IMPRESS I and II, with the intervention group showing significant improvement in both as opposed to placebo.³⁰ The value of these scoring scales was reconfirmed by Coyne and colleagues in 2015,³¹ who sought to verify the responsiveness of each scale. As defined by the authors, responsiveness is the ability of a patient-reported outcome scale to accurately reflect change in condition and truly differentiate between those who have in fact improved and those who have not. Information from subjects of the IMPRESS trials was used. During the course of IMPRESS, patients were to

complete baseline PDQ and GAPD assessment as well as at 24 and 52 weeks. In order to be included in the responsiveness survey, information from baseline and at least one follow up was necessary. The authors found that PDQ was able to discriminate between objective amounts of change and that increased improvement from baseline corresponded to improved PDQ scores. Changes of 20–50% in penile curvature resulted in significant improvements in terms of both psychological and physical symptoms scores as well as bother scores. As improvements in curvature exceeded 50%, improvement in PDQ became more pronounced. Such improvements also were found to correspond to improvements in GAPD score, suggestive of a correlation between objective improvement and patients' perception of PD impact on their life.

Ziegelmann and colleagues were among the first to collect information directly regarding patient-perceived improvements in physical characteristics as well as changes in functional outcomes following ILI.³² In a single-center, retrospective consecutive patient series, a total of 69 men underwent between one and four cycles of CCH between June 2014 and September 2015. Prior to ILI, preoperative penile characteristics were collected through both physical exam and penile ultrasonography. In addition, prior to treatment, all patients completed a PD-specific questionnaire to assess other aspects, including penile pain, ability to engage in sexual intercourse, self-perceived shortening, and subjective curvature. Their study group did differ in several respects including patients with calcified plaques and with stable disease for only 3 months or greater. During their study, each cycle consisted of two injections spaced 24–72 h apart of 10,000 U (0.58 mg) of CCH, with the cycles themselves 6 weeks apart. Patients were encouraged to self perform manual modeling by placing their penis on traction for 30 s each time they voided. They were also encouraged to place the penis on stretch between 1 h and 3 h daily. At each follow-up visit, patients completed an additional survey regarding their treatment thus far as well as the following subjective information: curvature change, percent change, and whether ILI had resulted in a meaningful improvement. At the time of analysis, 31 patients (45%) had completed four cycles of treatment. Of those men, 20 (74%) experienced at least a 20% objective improvement in degree of curvature as measured by a goniometer. Notably, of those same men, 88% noted subjective improvement in

terms of curvature and 81% felt the treatment was meaningful. Of this cohort, 52%¹⁴ had reported difficulty with vaginal intercourse initially. Following CCH, 57%⁸ of these patients felt that they were able to engage in sexual intercourse because of these injections. A majority of patients (52%)¹⁴ believed that CCH injections had prevented any surgical intervention and 33% stated they believed the injections had improved their penile sensitivity. After each cycle, questionnaires indicated subjective improvement in degree of penile curvature.

In an additional study by Anaissie and colleagues at a single institution, 77 men underwent ILI with CCH between April 2014 and March 2016.³³ Retrospective data were collected regarding their pretreatment characteristics such as degree of curvature and sexual function as well as treatment-associated characteristics, such as number of cycles, complications, and further procedures. These patients were subsequently contacted and asked to participate in a survey regarding their experience with CCH. Twenty-four of these patients ultimately agreed to participate in a survey regarding their experience with treatment. Questions were asked regarding self-perceived glans hypoesthesia, ability to have sexual intercourse, whether they would repeat the procedure, and overall satisfaction. Twenty-two of 24 patients (92%) were able to have intercourse following treatment compared with only 16 of 24 (67%) prior to treatment. Eight of 24 patients (33%) experienced glans hypoesthesia and 7 of 24 (29%) had at least a 20% decrease in their severity of curvature. Overall, 16 (67%) of the 24 patients surveyed were satisfied with their treatment. Dissatisfied patients on average had a greater decrease in curvature (17.6 *versus* 16.1) with fewer cycles of ILI (3.0 *versus* 3.7). Of note, no significant differences were found in any of the following areas when the satisfied and dissatisfied groups were compared: preoperative degree of curvature, preoperative pain, duration of PD, number of cycles, change in curvature complications, postoperative ability to have intercourse, and glans hypoesthesia.

Partner satisfaction

Equally scarce regarding the use of CCH are data regarding the satisfaction of men's partners following ILI. During the course of their above-mentioned study, Anaissie and colleagues also conducted surveys of 24 female sexual partners (FSPs) of men

who had undergone ILI over the previous 2 years. Data were collected regarding the PD sufferers' preoperative characteristics and then their FSPs were asked if they were overall satisfied with the procedure. In total, 17 (71%) of the 24 women surveyed expressed satisfaction with ILI. On retrospective analysis, no significant differences were noted in the male partners' preoperative characteristics for both satisfied and unsatisfied FSPs. The satisfied FSPs were less likely to have male partners with glans hypoesthesia, a potential side effect of ILI (18% *versus* 71%), while they were more likely to have a male partner with a history of penile trauma (44% *versus* 0%) and able to engage in sexual intercourse (100% *versus* 71%). Whereas six FSPs noted pain with sexual intercourse prior to ILI, this was reduced to four (20%) following treatment. No FSPs who experienced pain were unsatisfied with CCH overall. While no definitive reasoning for these characteristics being linked to improved FSP satisfaction was given, the authors did offer possible explanations. A history of trauma was explained as possibly being related to a feeling of responsibility in the FSP for the resultant penile curvature, with improvement leading to some alleviation of that guilt. Glans hypoesthesia and ability to engage in intercourse were suggested to relate to the sexual experience itself, with the former being detrimental and the latter improving it. The authors themselves noted multiple limitations of their study, including its small size and high dropout rate (68.9%), but noted it was the first of its kind and a possible foundation for future investigations.

Goldstein and colleagues completed a more recent study involving the partners of men undergoing treatment with CCH after having received placebo during the IMPRESS trial.³⁴ In a phase III open-label study, a cohort of 189 men received ILI with CCH with an administration schedule identical to that used during the trial. Patients received injections of 10,000 U (0.58 mg) spaced 24–72 h apart with two injections per cycle. Up to four cycles were completed, each 6 weeks apart. As with IMPRESS, coprimary endpoints were percent change in curvature as well as change in PDQ bother domain score. However, within this study, the authors also sought to assess the bother of FSPs as determined by two separate inventories: the PDQ for FSPs (PDQ-FSP) and the female sexual function index (FSFI). The PDQ-FSP is a 12-question nonvalidated, investigational survey adapted from the male PDQ administered to the FSPs of men afflicted with PD to quantify their perceived impact of the condition on their sexual

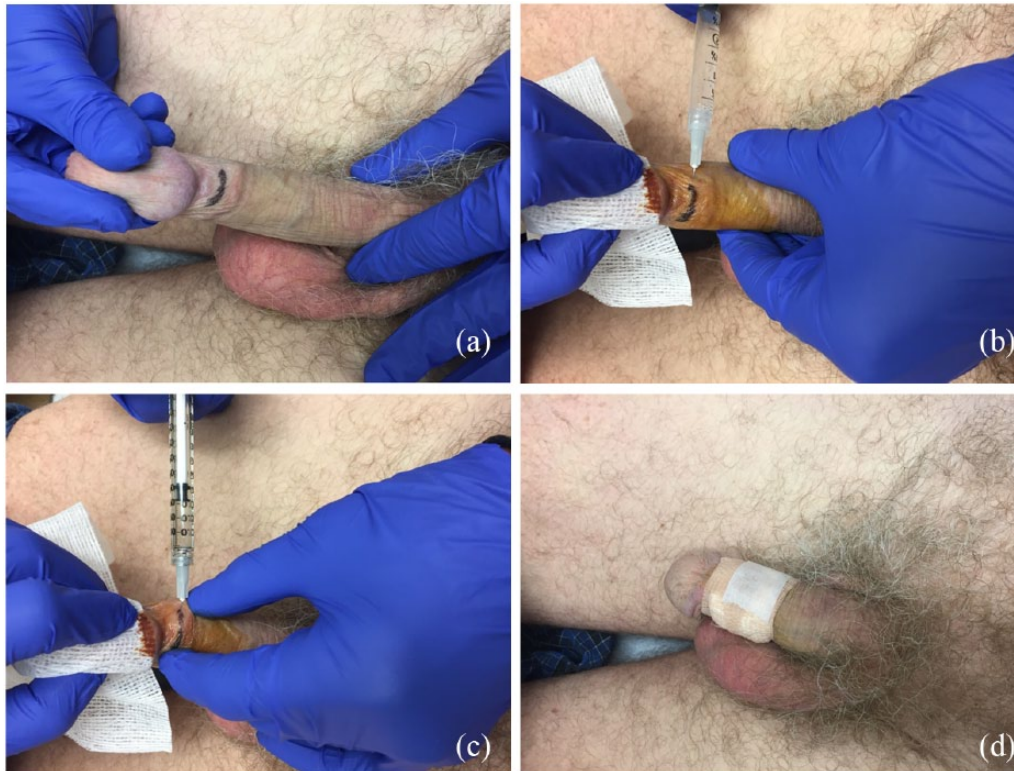


Figure 1. (a) Previous marking of the point of maximal curvature following intracavernosal injection of vasoactive agent allows the physician to identify the *Clostridium histolyticum* collagenase (CCH) injection location; (b) subcutaneous injection of local anesthetic is performed (physician preference); (c) intralesional CCH is injected into the plaque at the point of maximal curvature; (d) the penis is tightly wrapped with a dressing overnight to prevent hematoma formation (physician preference).

relationship. Questions concern the effect of PD on their partner's cosmesis, ability to engage in penetrative intercourse, and overall bother regarding the condition. The FSFI is a separate 19-question inventory assessing six separate areas (desire, arousal, lubrication, orgasm, satisfaction, and pain) central to female sexual function. Female partners completed these assessments at baseline and then once again at week 36. Ultimately, 30 FSPs elected to participate in the study, with the authors noting a low number due to poor recruitment and PD patient preference. Ninety percent of women involved were postmenopausal with an average age of 55.5. At baseline, men were more likely to be 'very' or 'extremely' bothered by the appearance of their penis, the effect of PD on vaginal intercourse, and perceived decrease in frequency of vaginal intercourse due to PD. Following treatment with CCH, FSPs reported a statistically significant decrease in PD impact on sexual intercourse (mean score decrease = 4.8; $p < 0.001$) and overall bother due to their partner's PD (mean decrease = 2.0; $p = 0.02$). Overall, 69.6% of

women stated that CCH improved their sex life and 56.5% reported improvement in their overall relationship following their partner's treatment with CCH. With regards to the FSFI, statistically significant improvements were seen in arousal, lubrication, orgasm, satisfaction, and pain. Overall FSFI scores were improved from baseline to week 36 (20.56 versus 26.72, mean change = 7.54; $p < 0.001$). The percentage of women who reported sexual dysfunction decreased from 75.0% at baseline to 33.3% after partner treatment.

Injection technique

Since its initial inception, injection techniques for CCH have remained relatively standardized. Two essential steps comprise the fundamentals of CCH injection: determination of the point of maximum curvature through induction of erection and injection of the CCH solution itself (Figure 1).

The technique consists of the following:

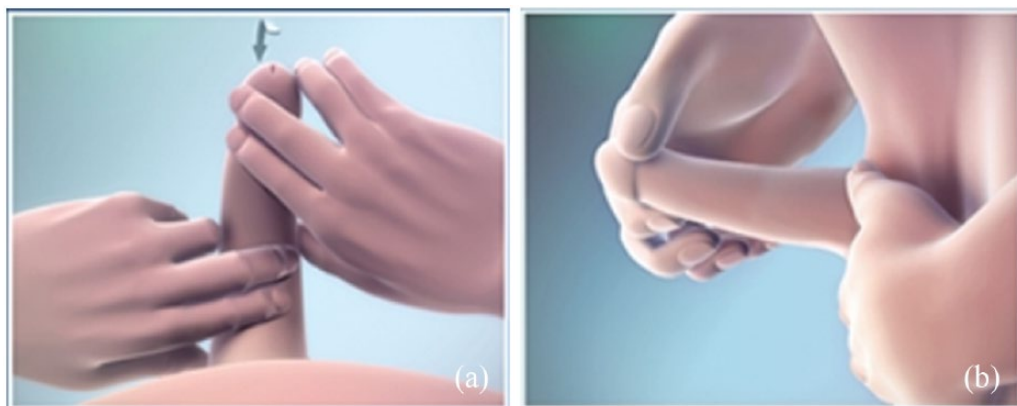


Figure 2. Between 48 and 72 h after each cycle of *Clostridium histolyticum* collagenase (CCH) injections, the patients are asked to perform manual modeling. (a) The flaccid penis is gently stretched three times a day. With one hand, the patient holds the tip of the penis and with the other hand he holds the base of the penis. The penis is gently pulled away from the body to its full length and holds the stretch for 30 s. (b) The erect penis is straightened once a day. This is only performed in the event of a spontaneous erection without sexual activity. The penis is gently bent in the opposite direction of the curve and is held in this more straightened position for 30 s.

- (1) Reconstitute CCH powder expressly as instructed according to package insert. CCH and the diluent should be allowed to stand at room temperature for at least 15 min prior to reconstitution. CCH should *only* be reconstituted with the provided diluent.
- (2) Prior to any injection of CCH, the point of maximum curvature should be determined on a patient through intracavernosal injection of a vasoactive agent. Once an erection has been induced, the penis should be visually inspected and the target site marked with a surgical marker
- (3) Apply antiseptic to the site of injection. If desired, local anesthetic may also be applied during this time.
- (4) Using a Hubless syringe with 0.01 ml gradations and a 27 gauge 1/2-inch needle, draw up 0.25 ml of the reconstituted solution.
- (5) With the penis in *flaccid* state, insert the needle into the edge plaque at a point in line with the point concavity. The point is to advance the needle through the plaque itself to the point of maximum concavity. Do not skive beneath the plaque or insert the needle perpendicularly so that it enters the corpus cavernosum.
- (6) Advance the needle so that it is at the opposite edge of the plaque. The goal is to inject the entirety of the 0.25 ml while simultaneously withdrawing the needle, depositing the entire dose within the plaque itself.
- (7) Once the needle has been withdrawn, apply gentle pressure and apply a dressing if necessary. All remaining solution should be discarded.
- (8) The second injection of any given cycle should be approximately 2–3 mm away from the first injection site.

Manual modeling

Manual modeling is a method of applying physical molding in order to reduce the severity of penile curvature and deformity. Since 2008, most studies have recommended at least some form of modeling provided by either a healthcare provider or the patient himself in order to augment the penile straightening process. Benefits of modeling have been shown previously in increasing the efficacy of CCH. For example, in a 2012 study by Gelbard and colleagues, a cohort randomized to receive CCH with no manual modeling showed no significant reduction in curvature compared with a group who received placebo (decrease in penile curvature of 27% *versus* 28% in placebo individuals of 28%²⁹).

Penile modeling is performed 1–3 days after the second injection of CCH in any given cycle. This serves to further stretch and elongate the PD plaque (Figure 2):

Table 3. Collagenase *Clostridium histolyticum* (CCH) studies for the management of Peyronie's disease (PD).

	No. of patients	Treatment regimen/protocol	Results
Gelbard <i>et al.</i> ²⁴	31	<i>Patients 1–6:</i> 3 consecutive days, 270–1595 U <i>Patients 7–31:</i> 3 consecutive days, 1739–4850 U	20 of 31 (65%) with objective improvement in penile curvature Resolution of preprocedural pain in 13 of 14 patients
Gelbard <i>et al.</i> ²⁷	49	Patient substratified into three groups: <i>Group 1:</i> <30° and plaque <2 cm (<i>n</i> = 7) <i>Group 2:</i> 30°–60° and 2–4 cm plaque (<i>n</i> = 24) <i>Group 3:</i> >60° and >4 cm plaque (<i>n</i> = 18) Patients received single injection of: Group 1: 6000 U Group 2: 10,000 U Group 3: 14,000 U	Significant improvement in curvature in group 2 only Response rates (in curvature and plaque size) compared with placebo were 100% <i>versus</i> 25% in group 1, 36% <i>versus</i> 0% in group 2, and 13% <i>versus</i> 0% in group 3
Jordan ²⁸	25	Three injections of 10,000 U over 7–10 days Follow up three injections after 3 months	Decreased penile curvature in 10/19 (53%) Plaque reduction in 18/19 (95%)
Gelbard <i>et al.</i> ²⁹	147	CCH <i>versus</i> placebo (3:1 ratio). Three cycles of two injections of 10,000 U (0.58 mg) CCH 24–72 h apart Three treatment cycles in 6 weeks Manual modeling	<i>Penile curvature</i> CCH: 29.7% (–16.3° ± 14.6°) Placebo: 11% (–5.4° ± 13.8°) <i>Modeling</i> CCH: 32.4% (–17.5° ± 15.3°) Placebo: 3% (0.6° ± 13.2°) <i>No modeling</i> CCH: 27% (–15.0° ± 14.0°) Placebo: 28% (–13.0° ± 10.7°)
Gelbard <i>et al.</i> ³⁰	<i>IMPRESS I</i> Total: 417 CCH: 277 Placebo: 140 <i>IMPRESS II</i> Total: 415 CCH: 274 Placebo: 141	Two 10,000 U (0.58 mg) injections, 24–72 h apart Four treatment cycles in 6-week intervals	<i>Penile curvature</i> CCH: mean 34.0% ± SD (–17.0° ± 14.8°) Placebo: mean 18.2% ± SD (–9.3° ± 13.6°) (<i>p</i> < 0.0001) <i>PDQ scores</i> CCH: 2.8 ± 3.8 Placebo: –1.8 ± 3.5 (<i>p</i> = 0.0037)
IMPRESS, Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies; PDQ, Peyronie's Disease Questionnaire; SD, standard deviation.			

- (1) Grasp the flaccid penis approximately 1 cm proximal and distal to the injection site (point of maximum concavity).
- (2) Using this as a focal point or fulcrum, use both hands to stretch and elongate the plaque by applying firm and steady pressure. The penis should be bent in a direction opposite the direction of curvature. Stretching should be carried out until the practitioner meets moderate resistance.
- (3) Once at moderate resistance, that position should be held for 30 s.
- (4) After 30 s, the stretching is relieved. There is a 30 s rest period and then the manual modeling is repeated again. Stretching should occur a total of three times, 30 s with each stretch.

In addition to the in-office modeling, patients themselves should be instructed to perform the following self-modeling at home during the intervening 6 weeks between cycles:

- During erections, straighten the penis without causing any pain and hold this position for 30 s.
- Stretch the flaccid penis three times per day with gentle steady pressure. Once again, this should be done without causing any discomfort.

Penile traction therapy

Penile traction therapy (PTT) is the application of external traction force, usually by way of an

external mechanical device, in order to stretch the penis.³⁵ Although PTT has been previously used for multiple purposes, its use in the treatment of PD is a relatively recent phenomenon. Previous histologic studies have demonstrated the application of mechanical forces as found in PTT can lead to preferential reorganization of disordered collagen fibrils.³⁶ Moreover, given its previous use of Dupuytren's contracture, several studies have employed PTT both as a monotherapy and in conjunction with other treatments. Despite its noninvasive and novel nature, experience with PTT combined with intralesional therapy is limited. Two previous studies demonstrated improvements in penile length but non-significant changes in terms of degree of curvature for patients with PD who underwent PTT combined with both a combination of arginine, pentoxifylline, and verapamil³⁷ as well as interferon.³⁸

To date, Ziegelmann and colleagues have been the only group to investigate the role of PTT in combination with CCH therapy for the treatment of PD.³⁹ At a single site from March 2014 to July 2016, a total of 120 men underwent ILI with CCH for treatment of PD. Initial evaluation included physical exam, duplex ultrasonography of the penis, and evaluation of curvature after administration of erectogenic medication. All patients had dorsal, lateral, or dorsolateral curvature between 30° and 90°, adequate erectile function, and an identifiable plaque on examination. Men with minimally calcified plaques were included in the study. Patients underwent two injections per cycle of CCH spaced 24–72 h apart for up to four cycles with each spaced 6 weeks apart. Patients themselves were encouraged to perform 'aggressive' manual modeling for 30 s with each void. Additionally, patients were instructed to apply PTT daily using a traction device. After completion of four cycles of CCH, data regarding penile curvature, stretched penile length (SPL), and frequency of PTT were collected. Additionally, patients were asked if injections had restored their ability to engage in penetrative intercourse and whether CCH had obviated the need for surgery. Of the initial 120 patients, 51 men had completed four full cycles of CCH. Twenty-one (18%) patients of the initial cohort were lost to follow up during this time. Men were analyzed as a total cohort and then further subdivided into patients who performed PTT (PTT +) and those who did not

(PTT -). Overall, men undergoing CCH experienced a significant improvement in penile curvature with a composite curvature reduction of 34.1° (27%; $p < 0.0001$) for the entire cohort. There was no significant difference in change in curvature (19.6° versus 23.6°; $p = 0.30$) or SPL between the PTT (+) and PTT (-) cohorts (0.4 cm versus -0.35 cm; $p = 0.21$).

Specifically regarding PTT, only 3 (8.6%) of the PTT (+) cohort performed at least 3 h of therapy per day. Notably, of those who did perform the recommended duration and frequency of PTT, there was no significant difference in their improvement in penile curvature ($p = 0.93$). Subjectively, 82% of the PTT (+) cohort and 85% of the PTT (-) cohort felt their CCH therapy had proven meaningful. No significant differences were found in restoration of penetrative intercourse (69% versus 57%; $p = 0.8$), prevention of surgery (55% versus 43%; $p = 0.86$), or subjective improvement in curvature (31.4% versus 42.2%; $p = 0.42$).

Administration schedule

Early treatment regimens with CCH varied significantly both in terms of dosing as well as schedule. In his initial trials, Gelbard administered varying doses of CCH 3 days consecutively, dosages depending on the severity of curvature.²⁴ Jordan utilized a similar regimen in his 2008 study, administering three courses over 7–10 days, albeit with an identical dose of 0.58 mg.²⁸ However, beginning with phase IIb trials in 2012 and continuing with the IMPRESS trials in 2013, administrations schedules have become largely standardized.

Currently, the IMPRESS treatment regimen is considered the *de facto* standard administration schedule and that which is recommended by the manufacturer.^{30,40} With this schedule, a patient receives an injection of CCH, followed by a second injection 24–72 h later. These two injections are considered a single cycle. Six weeks are recommended between cycles at which point the patient is followed up. If the patient and his physician at that time feel the amount of improvement or current curvature is acceptable (e.g. <15°), no further injections are necessary. However, if a second cycle is desired, this can be repeated with a day's duration between injections. Up to four cycles can be completed, each with 6 weeks intervening.

Abdel Raheem and colleagues published a trial offering an alternative injection schedule to the traditional pattern of two separate injections, 24–72 h apart. In their reasoning for publishing the study, the authors noted that the traditional protocol is uncomfortable and demanding for the patient as well as technically difficult for the physician, with the PD plaque often obscured by hematoma or swelling at the second office visit.⁴¹ To address these issues, the authors instead recommend the injection of an entire vial (0.9 mg) during a single setting at three discrete sites surrounding the plaque: at the plaque's most proximal point, at the point of maximum curvature, and at its most distal point. Additionally, rather than employing physician manual modeling, patients are provided with a home vacuum erectile device. Patients attend a total of four office visits over 14 weeks as opposed to 14 over 24 weeks in the traditional regimen.

In their series of 53 patients in whom the modified regimen has been used thus far, the authors noted 51 (96.2%) of these men demonstrated improvement in curvature. The mean improvement was 17.36° (31.4% from baseline). Forty-five (85%) of these men reported subjective improvement on a GAPD questionnaire with no complications. Although utilized in only one series with limited patient volume, this protocol may provide an alternative regimen which is significantly less burdensome to patients and physicians alike. Further evaluation is necessary to determine the role such an expedited schedule may play in future CCH treatment.

Off-label administration

In their initial IMPRESS trial, as detailed previously, the authors were highly selective with their patient population. Numerous forms of atypical PD were specifically excluded, homogenizing the cohort but also potentially marginalizing a number of men suffering from PD who could benefit from treatment. Given these exclusions from the study, at the time of FDA approval in 2013, similar exclusions were made, forcing treatment of men with these atypical forms of PD to be marked as off label. Preliminary investigations of CCH for several of these groups have been made to evaluate the safety and efficacy of this therapy.

Acute phase disease

PD is defined by two distinct phases: an active or acute phase characterized by progression in

curvature and symptoms like pain, followed by a quiescent phase wherein both symptoms and progression stabilize.^{11,42} During the course of IMPRESS, patients were required to have had stable PD for at least 1 year or longer to be eligible for treatment.³⁰ Multiple potential reasons for this exist, including avoidance of further curvature following correction and a theoretical increased risk of side effects like corporal rupture due to a weakened tunical wall. Accordingly, the AUA guidelines recommend stable disease for at least 1 year and use of CCH in patients with acute phase disease is at this time still considered off label.^{21,40}

ILI with CCH has been performed in patients with shorter duration quiescent disease and active disease. Ziegelmann and colleagues included men who had stable disease for as little as 3 months during their 2016 analysis, with no complications among this cohort.³² Yang and Bennett included a cohort of patients with active phase disease, by their definition, changes in curvature or symptoms within 12 months prior to the first CCH injection, during their 2016 series.⁴³ This group experienced no difference in rate or severity of complications and were found to have a significant difference in the mean reduction in curvature compared with patients with stable disease (20° versus 13.9°; $p < 0.001$). Given this amount of change, the authors suggested CCH may have some role in affecting the progression of acute phase disease and recommended further study.

In a second, larger series, Nguyen and colleagues similarly analyzed the use of CCH in active phase disease.⁴⁴ In a single-site retrospective analysis of patients who underwent treatment with CCH between April 2014 and April 2017, from a total of 162 patients, 36 (22%) were found to be in the active phase, defined as changes in curvature or symptoms in the 12 months prior to the first injection. Following ILI, retrospective data were collected regarding baseline characteristics and post-treatment degree of curvature, SPL, International Index of Erectile Function (IIEF) scores, and other treatment outcomes such as complications or further interventions. The primary endpoint was change in curvature following treatment with CCH, with secondary endpoints of IIEF score, change in curvature after the first cycle, and change in penile length. Points of maximal curvature were determined following injection of alprostadil, with all patients having at least 30° curvature. Patients were standardized to a typical IMPRESS protocol schedule of CCH

injections. All patients underwent penile modeling beginning 24–72 h after the second injection of each cycle.

On retrospective analysis, patients were subdivided into two groups: those with active disease and those with stable PD. The median duration of PD for the active group was 8.5 months while the median duration for the stable group was 18 months ($p = 0.009$). Aside from duration of disease, there were no statistically significant differences between groups, including degree of curvature or IIEF scores. Following treatment, curvature in the cohort as a whole improved from a mean 57.7° to 41.9° ($p < 0.001$). There was no statistically significant change in final curvature (16.7° versus 15.6° ; $p = 0.654$), IIEF scores (1.6 versus -1.0 ; $p = 0.15$), or SPL (0.5 versus 0.1 ; $p = 0.315$) between the active phase and stable phase groups after treatment. Additionally, no statistically significant difference was found in frequency of complications between groups (active = 4, 11% versus stable = 13, 10%; $p = 0.356$). Although not currently approved, such data provide a compelling argument for expansion of indications and labeled usage of CCH in the future.

Ventral plaque

PD plaques typically manifest themselves in a dorsal or lateral position, with plaques on the ventral surface being relatively uncommon. These occur in about 9% of patients with PD and typically manifest with downward curvature of the penis.⁴⁵ During the IMPRESS trials, ventral plaques were an exclusion criterion owing to the authors' concern regarding injury to the urethra with injections.³⁰ As with other forms of atypical PD, use of CCH in patients with ventral Peyronie's plaques is considered off label. Yang and Bennett did include a single patient with ventral curvature in their initial retrospective series.⁴³ Unfortunately, no specific information was given regarding this patient, including change in curvature, erectile function, or adverse events. In a scientific abstract presented at the Sexual Medicine Society of North America (SMSNA) in 2015, Milam described the treatment of two patients with ventral PD using CCH.⁴⁶ His results found encouraging effects from ILI, with both men demonstrating improvement (from 45° to 5° and from 30° to 5 – 10°) and without any significant side effects from local bruising and discomfort or harm to the urethra aside. Besides these two limited queries, minimal information exists regarding use of CCH in

patients with ventral curvature. ILI for such patients remains uninvestigated and requires further study.

Hourglass deformity

Hourglass or 'notching' deformity is the presence of bilateral narrowing and the appearance of a bottleneck at a discrete level on the penile shaft secondary to penile plaque.^{47,48} Occurring in about 1% of patients with PD, hourglass deformity has been associated with diminished peak systolic penile velocities, arterial insufficiency, and erectile dysfunction in as many as 68% of sufferers.⁴⁹ As with ventral deformity, information regarding the use of CCH with hourglass deformity is limited. Eleven (22.4%) of the patients included in the study by Yang and Bennett suffered from hourglass deformity. However, as with ventral curvature, no specific information is given regarding this subset in their study. Further investigations are required in order to assess the efficacy of CCH in these patients.

Calcified plaque

Calcification is a common finding in stable PD, often occurring once progression of the plaque has stopped and scarring has entered a quiescent phase.^{5,6} Frequently, increasingly calcified plaques are more easily palpable on physical exam. Patients with complete calcification were excluded from study during IMPRESS due to concern that this could potentially lead to interference with injection of the medication itself. Patients with partial or stippled calcification were allowed. Results have varied regarding the effect of calcification on CCH injection, with multiple studies including patients with partially calcified plaques in their treatment populations and noting no significant difference between these patients and noncalcified plaques.^{32–34,38,39}

In contrast, in a study reviewing subgroups from the IMPRESS I and II trials, differing effects of CCH based on the severity of calcification were discovered.⁴⁹ In this analysis, Lipshultz and colleagues targeted specific subpopulations from the cohort to determine if other factors had modified the impact of ILI. The primary outcomes of the trial, changes in penile curvature and reduction in PDQ bother scores, were their points of focus. Among the groups reviewed were men with plaque calcification compared with men with none. Information regarding calcification was available

in 612 of the original 812 patients in the study, with 447 having no calcification, 103 with noncontiguous stippling, and 62 with contiguous calcification which did not interfere with CCH injection.

With regard to penile curvature, the authors found significant improvement in the no calcification group when comparing those who received CCH *versus* placebo ($-34.3\% \pm 28.0\%$ *versus* $-16.8\% \pm 28.3\%$; $p < 0.001$). Although curvature was reduced for men with calcified plaques, this was found to be nonsignificant for both the stippled group ($-35.9\% \pm 27.0\%$ *versus* $25.5\% \pm 33.0\%$; $p = 0.110$) and the contiguous calcification group ($28.0\% \pm 28.7\%$ *versus* $19.5\% \pm 24.3\%$; $p = 0.231$) *versus* placebo. Similar findings were noted in the PD bother score assessment, with significant changes found in the noncalcified group (-2.9 ± 3.8 *versus* -1.7 ± 3.5 ; $p < 0.001$) and nonsignificant changes in both the stippled (-2.6 ± 3.6 *versus* -1.8 ± 3.9 ; $p = 0.342$) and contiguous calcification (-2.7 ± 3.7 *versus* 2.7 ± 3.5 ; $p = 0.985$) groups. Of note, the authors did caution against drawing specific conclusions from these findings given the relatively small populations within the calcified groups.

Safety considerations

Although safe overall as a therapy, CCH has been associated with a number of potential adverse events.^{22,30} In a pooled analysis of 1044 patients across six trials including IMPRESS I and II, at least one treatment-related adverse event (TRAE) was reported by 86% of males receiving CCH. Most TRAEs were minor or moderate in severity (87%) and resolved without intervention (79%). Most common among TRAEs were penile pain, ecchymosis, and edema, each occurring in at least 25% of the pooled patient population. Serious adverse events (SAEs), defined as those requiring inpatient hospitalization, surgical intervention, life-threatening situations, permanent disability, or death, were present in only nine patients. Of these, five SAEs were penile hematoma and four corporeal rupture which required surgical repair. As a biological molecule, severe allergic reaction or anaphylaxis has been suggested as a potential serious consequence of CCH therapy. When antibody titers were collected, over 95% of patients did develop antibodies to AUX-I and AUX-II by the conclusion of their treatment. However, despite this immunologic reaction, no patients developed a systemic immunological response or discontinued therapy due to this.^{22,30}

Take home messages

CCH offers a less invasive approach, compared with surgery, for the management of PD. The current guidelines and indications are limited to patients with stable disease, a nonventral curvature or hourglass deformity. Patients with PD are often quite troubled by their condition, so proper counseling about treatment expectations is paramount to treatment satisfaction and continuation. While CCH may not be as efficacious as surgery, it can be offered to motivated patients as a first option and, if the treatment is unsuccessful, reports indicate that surgery can be safely performed afterwards. Finally, it is imperative that patients be counseled at length about serious TRAEs such as hematoma, pain and, more importantly, corporal rupture.

Conclusion

CCH is an effective and noninvasive means of treating many men with PD. As a recent form of therapy, ongoing research and trials have continued to expand the population of patients, define the method and timing of injections, and clarify adjunct practices which could serve to augment its therapeutic effect. Through proper patient selection and proven technique, ILI with CCH has thus far demonstrated a profound ability to diminish the effect of a condition with marked physical and psychological symptoms. This review serves to demonstrate studies thus far validating the effect of CCH, highlighting areas for further investigation and detailing its best current use. With ongoing refinement of this therapy, CCH will continue to advance as a major means of reducing the burden of PD.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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