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Abstract

Objectives: Peyronie's disease (PD) is a connective tissue disorder resulting in the abnormal accumulation of scar or plaques in the tunica albuginea of the penis. The condition is characterized by two phases: an active, inflammatory phase, and a stable, chronic phase. Collagenase *Clostridium histolyticum* (CCH) was isolated in the mid-1900s and postulated as a potential pharmacologic strategy for breaking down the abnormal connective tissue plaques of PD. Prior to the introduction of CCH, a wide variety of treatment modalities for PD were used in clinical practice, including oral and topical medications, intralesional injections, electromotive drug administration, extracorporeal shockwave therapy, traction, and invasive surgery, all with variable results. This review aims to examine the known data surrounding the use of intralesional CCH injections in the treatment of PD.

Methods: CCH is a recently US Food and Drug Administration approved pharmacologic treatment for PD. Clinical trials using intralesional CCH injection therapy for the treatment of PD were reviewed for clinical safety and efficacy of treatment.

Results: Studies demonstrated that CCH treatment administered in multiple cycles led to significant benefit in both the psychological and physical aspects of PD. The strongest evidence for CCH's effectiveness was revealed in large, multicenter randomized controlled trials (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies I and II) in which intralesional CCH was combined with manual modeling of the penis. Although adverse events from treatment are relatively common, the majority are mild to moderate in degree, including penile pain, swelling, and bruising, which all resolve spontaneously.

Conclusion: Overall, evidence indicates that CCH is a valuable, effective, and safe minimally invasive treatment option for men with PD.

Keywords: Collagenase *Clostridium histolyticum*, penile plaque, penile curvature, Peyronie's disease, Peyronie's Disease Questionnaire

Background

Francois de La Peyronie was credited more than 250 years ago with describing what is now known as Peyronie's disease (PD), a connective tissue disorder characterized by an inelastic fibrous plaque that forms within the tunica albuginea of the penis [Dunsmuir and Kirby, 1996]. Recent evidence suggests that the prevalence of this disease is higher than previously thought [Schwarzer *et al.* 2001]. In 1991, Lindsay and colleagues postulated a prevalence of 388.6 cases of PD per 100,000 male patients after reviewing the total number of cases in Rochester, MN between 1950 and 1984 [Lindsay *et al.* 1991]. In recent years, studies have shown that the true prevalence of this condition can range from 3.2% to 13% [Sommer *et al.* 2002; Dibenedetti *et al.* 2011]. In a study of patients with diabetes and erectile dysfunction, 20.3% of the participants had PD [Arafa *et al.* 2007]. In a population-based study of 16,000 men aged 18 years or older, it was reported that up to 13% of patients had symptoms and signs of PD. Older men (average age of 52.7) were most affected. Actual diagnoses of PD by physicians in this group was only 0.5%, suggesting that PD is underdiagnosed and undertreated

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[Dibenedetti *et al.* 2011]. Furthermore, in recent years, there have been a greater number of younger patients presenting with PD. A recent study found 17% of patients to be under the age of 40 [Paulis *et al.* 2015].

PD was first described in a published report in the eighteenth century, but the pathogenic mechanisms of the disorder are still poorly understood. It is believed that PD is a wound healing disorder caused by excess inflammation and subsequent collagen deposition. However, the origin of this inflammatory process has not been established. One study, that compiled survey results from 207 men who had been treated for PD, indicated that 40% of patients had suffered some form of penile trauma [Jarow and Lowe, 1997]. Although trauma is a precipitating factor for a significant number of PD cases, one retrospective review of 408 patients cited a family history of PD in 1.8% of cases. The same review revealed that an estimated 15.7% of these patients were also affected by Duyputren's contracture. Together, these data showed a total of 17% of cases could be attributed to genetic factors [Chilton *et al.* 1982; Ralph *et al.* 1997; Nyberg *et al.* 1982]. Recently, there has been evidence suggesting an increased risk of PD in patients with diabetes mellitus [Kendirci *et al.* 2007]. Finally, decreased testosterone has also been implicated with causing more severe PD symptoms [Moreno and Morgentaler, 2009].

Histologically, it is believed that trauma to the tunica albuginea leads to inflammation and disruption of the normal cell architecture. Trauma-induced cytokine signaling can then result in fibrin deposition. Macrophages and other inflammatory cells that enter this tissue secrete transforming growth factor β (TGFβ), which, in turn, stimulates collagen synthesis. Fibrin also causes an increase in TGFβ1 [Paulis and Brancato, 2012]. TGFβ1, in particular, is hypothesized to play a role in PD since in a histological study of tunica samples of 30 patients with PD, 26 (86%) had TGFβ1 expression, whereas only 7 (23%) and 5 (17%) had TGFβ2 and TGFβ3 expression, respectively; control subjects' tissue had no expression of these proteins [El-Sakka *et al.* 1997]. In addition, fibrin increases plasminogen activator inhibitor 1, which inhibits the matrix metalloproteinases that break down collagen. The potential importance of modulation of matrix metalloproteinase expression in the progression of PD was investigated in cultured fibroblasts and showed that TGFβ induced the expression of tissue inhibitors of matrix metalloproteinase (TIMPs) [Del Carlo *et al.* 2008]. Immunological studies using tunica samples from PD plaques revealed that diseased plaques were highly enriched with TIMP1-4 compared with nondiseased tunica [Del Carlo *et al.* 2008]. Both TGFβ1 and fibrin have been shown to induce PD in animal models. Davila and colleagues revealed that injection of fibrin into the tunica albuginea of rats induced the development of a fibrous plaque histologically similar to those observed in patients with PD [Davila *et al.* 2003].

PD is divided into acute and chronic phases. In the acute phase, patients present with a palpable fibrous plaque in the tunica albuginea, likely involving the inflammatory mechanisms described above. Development of the plaque can be accompanied by penile pain, regardless of flaccidity or erection. In addition, the evolving plaque causes worsening penile deformities, such as increasing penile curvature, narrowing, and shortening. Resolution of this phase occurs when the plaque stabilizes and the pain usually subsides. The ensuing stable or quiescent phase may occur anywhere between 6 months and 2 years after onset of PD [Berookhim *et al.* 2014]. During this stage, penile deformities may progress. Previously, it was generally believed that PD resolved on its own in the majority of patients. However, an analysis of the progression of untreated PD was found to refute that concept. Only 12% of patients showed improvement in penile curvature within 1 year of diagnosis, while 48% of patients had worsening curvature [Mulhall *et al.* 2006]. Complete resolution of deformity is rarely reported.

Furthermore, PD has a tremendous impact on the psychological well-being of patients. In a study evaluating depression in patients with PD, it was noted that 48% of patients diagnosed with PD had depression, with 26% classified as moderate and 21% as severe [Nelson *et al.* 2008]. Patients with PD also experience emotional distress such as sexual anxiety, fear of forming relationships, feelings of shame, and loss of control of personal life [Rosen *et al.* 2008]. As a result, this may contribute to the low diagnostic rate of PD, as patients may choose to conceal their condition from their doctor. Due to the importance of evaluating these types of subjective issues in men with PD, the Peyronie's Disease Questionnaire (PDQ) was developed as the first PD-specific systematic, validated questionnaire designed to quantify patients'

psychosexual symptoms [Hellstrom *et al.* 2015]. The PDQ consists of 15 questions in three independent domains: Peyronie's symptom bother, Peyronie's psychological and physical symptoms, and penile pain. Psychosexual evaluation of patients in addition to physical examination is essential to patient care; in one study, when subjects were subdivided into subgroups by degree of curvature, the extent of psychosexual symptoms individuals experienced and how these symptoms changed after treatment was not simply correlated with the degree of penile curvature [Hellstrom *et al.* 2015].

Current treatments

PD has traditionally been a difficult condition to treat. Treatment seeks to disrupt the inflammatory reactions and collagen plaque formation. Due to the difficulty of treating PD, a wide variety of treatment modalities have been proposed; such as oral, electromotive, injectable, and surgical therapies. Surgery remains the gold standard, but is only considered in patients who have reached the stable chronic phase after at least 12 months [Tan *et al.* 2014]. Oral therapies consist of vitamin E, potassium paraminobenzoate, tamoxifen, colchicine, carnitine, and phosphodiesterase inhibitors and have, overall, shown underwhelming clinical efficacy in treating PD [Mynderse and Monga, 2002; Hellstrom, 2009]. Transdermal electromotive drug therapy has also been attempted to bypass hepatic metabolism of oral therapies and to increase penetration of topical medication such as verapamil [Stancik *et al.* 2009; Greenfield *et al.* 2007]. Intralesional treatments with interferon α and verapamil have been described, and have been shown to decrease penile pain and curvature [Hellstrom *et al.* 2006; Trost *et al.* 2013; Stewart *et al.* 2015; Chung *et al.* 2013].

Intralesional CCH is the only US Food and Drug Administration approved treatment for PD and offers a nonsurgical approach to treating this condition. Injections of CCH are administered directly into the tunica albuginea at the site of the PD plaque where maximum curvature is observed. Following injection therapy, the patient undergoes penile modeling consisting of manual manipulation of the flaccid penis using gentle, progressive stretching in a direction opposite to that of penile curvature, with the intention of stretching the abnormal collagen fibrils in the penile plaque.

Collagenase *Clostridium histolyticum*

Mechanism of action

CCH has been investigated as a pharmacologic treatment for PD for a few decades. An *in vitro* study performed in 1953 was the first to isolate the proteinase and collagenase enzymes from *Clostridium hystolitica* culture and characterize their activity and stability, noting that the proteinase enzyme was not active against collagen fibrils [Mandl *et al.* 1958]. It was observed that the collagenase was active in degrading collagen types I and III, commonly found in bone, connective tissue, and scar tissue, but spared type IV, which is localized to vascular and nervous tissue. CCH enzyme is maximally active at a pH of 7.4 in a phosphate buffer and is inhibited by high cysteine concentrations. Both the proteinase and collagenase showed no activity against elastin, keratin, egg albumin, hemoglobin, or bovine serum [Levine *et al.* 2014].

CCH has been investigated since 1966 as a treatment option for Dupuytren's contracture, a pathology closely related to PD that causes a progressive deformity of the hand due to connective tissue contracture [Desai and Hentz, 2010]. Although surgery remains the gold standard of treatment for Dupuytren's contracture, CCH was recently licensed as a nonsurgical treatment for this condition, having been shown to degrade collagen lesions while sparing neurovascular structures. Similar to its use in PD, CCH in this setting is injected directly into the Dupuytren's cord, and the procedure is followed by manual rupturing of the cord 24 h post injection [Holzer and Holzer, 2011]. Multiple trials including two large, prospective, double-blind, placebo-controlled trials have demonstrated that patients treated with CCH showed significant reduction in contracture compared with those who received placebo; CCH treatment was generally well tolerated with adverse events being mostly self-limited [Kaplan, 2011].

In 1982, the first pilot study to examine the utility of purified CCH for the management of PD revealed promising results. The study described the dose-dependent activity of CCH and found no selective effect on PD plaque tissue over normal tunica albuginea tissue. In addition, the study observed that most collagen breakdown occurred within the first 24 h of incubation with a mean decrease in tissue weight of 88.6% in CCH samples compared with 9.3% in control samples [Levine *et al.* 2015]. A study outlining

the proteolytic activity of CCH on type I collagen in rat tendons divided CCH enzymes into class I (AUX-1) and class II (AUX-II) and elucidated the distinct cleavage differences between the different classes of collagenases. Class I collagenases initially cleave collagen at hyperactive sites near the C terminus followed by a site near the N terminus; class II collagenases behaved similarly to mammalian collagenases, with the first cleavage site being at a hyperactive site at an internal location across all three chains, producing two large cleavage products [French *et al.* 1987].

Pharmacology

The pharmacokinetics of CCH were examined in a study of humans; subjects received two intralesional injections of 0.58 mg at 24 h apart and plasma level measurements were obtained for AUX-I and AUX-II [Levine *et al.* 2015]. Of patients with quantifiable levels, maximum plasma concentrations of AUX-I and AUX-II collagenases were measured at 10 min following injections at $<$29 ng/ml and $<$71 mg/ml, respectively, with measurements falling to undetectable levels at 0.5 h post injection. None of the subjects had detectable levels of AUX-I or AUX-II at the time of penile modeling on day 3 of the study [Levine *et al.* 2015]. No studies exist that have examined the metabolism of CCH; it does not produce active metabolites and is not metabolized by cytochrome p450 enzymes.

Safety and tolerability

The safety of CCH was assessed in several early animal studies evaluating the applications of collagenase in intervertebral discolysis to treat herniation. These studies found no adverse hematologic effects on erythrocytes, leukocytes, or platelets and no other adverse systemic effects when administered to dogs at 100 times the prospective therapeutic dose [Sussman and Mann, 1969]. Rat studies at high doses similarly found no adverse systemic effects of CCH, including fertility and harm to fetus, when administered up to 11 times the maximum recommended human dose (MRHD). Liver toxicity and death were observed at doses greater than 11 times and 25 times the MRHD, respectively [Garvin, 1974]. In a more recent study, no systemic effects were observed in rats or dogs during a 13-week subcutaneous repeat dose study at three times the MRHD; systemic effects were also not observed in dogs in a single-dose phase and 61-day-repeat-dose phase of intrapenile administration of CCH at or below the MRHD [Auxilium Pharmaceuticals Inc., 2014].

Numerous clinical trials have demonstrated CCH as an acceptably safe therapeutic treatment for PD. The initial study demonstrating safety was conducted in 1985 in which variable doses of CCH intralesional injections were generally well tolerated by 31 subjects, with no systemic effects reported, 21 patients reporting ecchymosis, two reporting pain at the injection site, and one who experienced corporal rupture during intercourse 2 weeks following the injection [Gelbard *et al.* 1982]. In 1993, a follow-up, double-blind randomized controlled trial reported no allergic reactions or serious adverse events in 49 patients studied. One treatment patient had a small tunica albuginea tear, determined based on a popping sound heard during intercourse and a small amount of ecchymosis seen after the event, which self-resolved with conservative treatment. Patients receiving CCH treatment reported tenderness at the site of injection as frequently as those receiving placebo injections [Gelbard *et al.* 1993]. In 2008, a follow-up safety study was conducted as a prospective phase II trial. Out of the 25 subjects, 20 patients (80%) showed adverse events that were mild to moderate in severity; primarily penile edema, pain, and ecchymosis, and all resolved spontaneously [Jordan, 2008].

A phase IIb trial involving 147 patients further characterized CCH as a safe and effective nonsurgical treatment for PD. A total of 137 (93%) patients received all planned injections; adverse events caused only two patients to stop treatment. This trial identified that the majority of adverse events were mild to moderate in severity and included injection site bruising, edema, and pain; these adverse events were observed to occur statistically significantly more often in subjects receiving CCH treatment than those receiving placebo, with a higher rate of bruising (86.5% *versus* 45%), edema (44.4% *versus* 0%), and pain (52.3% *versus* 11.1%). Less common adverse events were not specific to the injection site and included penile pain (9.9%), penile edema (9.9%), and painful erections (4.5%). At the conclusion of treatment, after completion of injections, the majority of patients (95%) did have antibodies to both AUX-I and AUX-II, but there was no evidence of a systemic immunologic reaction to CCH in any patient [Gelbard *et al.* 2012].

Two subsequent phase III trials, Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies I and II (IMPRESS I and II), again evaluated the safety and efficacy of CCH injections in the treatment of PD and had findings similar to previous studies [Gelbard *et al.* 2013]. The maximum treatment cycle of eight injections was given to 434 of 551 patients in the treatment arm and 247 of 281 of those in the placebo group. As many as 464 subjects (84.2%) experienced adverse events, typically mild to moderate, localized to the penis compared with 102 (36.6%) in the placebo arm. The majority (79%) of adverse events resolved with conservative management; as with the previous trial, the most commonly occurring adverse events included penile ecchymosis (80%), penile edema (55%), and penile pain (45.4%). More serious adverse events included three corporal ruptures and one hematoma, which were successfully treated with surgical interventions. Similar to the previous study, the majority of patients who received CCH treatment had positive anti-AUX-I and anti-AUX-II antibodies (75% and 53.4%, respectively) after the first cycle of injections; at 1 year from the start of the trial, almost all patients were producing anti AUX-I and anti-AUX-II antibodies (99.2% and 98.4%, respectively). As with the previous studies, there were no reports of systemic immunologic reactions or reactions to treatment [Gelbard *et al.* 2013].

One trial specifically aimed to address the extent of immunologic reaction to CCH injections by measuring immunoglobulin G (IgG) and IgE antibody levels in sera of a control group of 150 healthy blood donors, and a treatment group of 44 patients who were receiving CCH for PD. Radioimmunoassays were performed 1–2 months following treatment; IgG levels increased 2 to 10-fold in 88% of patients, whereas only 0.5% of patients (one subject) had detectable levels of IgE against collagenase. These results concur with previous trials' conclusions regarding immunologic reaction to collagenase. In fact, only one nonfatal anaphylactic reaction to CCH has been documented; the patient had previously been exposed to CCH in the context of Dupuytren's contracture treatment [Auxilium Pharmaceuticals Inc., 2014]. Due to this rare, adverse event, a history of severe allergic reaction to CCH is a contraindication to future treatment [Gelbard *et al.* 2015].

A meta-analysis that included six studies, three of which were randomized controlled trials, analyzed the overall known data regarding adverse events and safety of CCH for the treatment of PD in 1044 total pooled patients. Their analysis found that 85.8% of patients reported at least one treatment-related adverse events, and that the vast majority of these cases (75.2%) were mild to moderate in severity. As previously mentioned, the events associated with treatment that occurred most frequently were penile hematoma (82.7%), penile pain, and penile swelling. Only nine patients (0.9%) experienced CCH-related adverse events that were significant: penile hematoma (five patients) and corporal rupture (four patients). Severe adverse events were rare, and all cases of corporal rupture were in patients who had engaged in sexual intercourse within 31 days of intralesional CCH injections. As a result of this finding, it is recommended that patients do not have sexual intercourse for at least 2 weeks following CCH injection [Auxilium Pharmaceuticals Inc., 2014]. Adverse events were not correlated with anti-AUX-I and anti-AUX-II antibody production, and there were no cases of systemic allergic reactions. This meta-analysis convincingly shows that while CCH is associated with a significant number of adverse events, these events are predominately mild to moderate in severity and resolve quickly with conservative treatment [Carson *et al.* 2015].

Efficacy

The efficacy of CCH in the treatment of PD has been extensively evaluated through clinical trials, and a comparison of these studies is outlined in Table 1. In 1985, Gelbard and colleagues conducted the first phase I clinical trial of 31 patients who received varying doses of CCH [Gelbard *et al.* 1985]. Response to treatment, including effect on plaque size, penile curvature and penile pain, were recorded. Six patients received three consecutive days of intralesional CCH injections; dosing ranged from 0.027 mg to 0.093 mg (mean 0.047 mg). The 25 remaining patients received a combination of daily intralesional CCH injections, with doses ranging from 0.101 mg to 0.281 mg (mean 0.156 mg) and adjuvant B-aminoproprionitrile fumberate (BAPN-F) therapy, a proposed lysyl oxidase inhibitor. BAPN-F was intended to increase collagen laxity; however, it was not considered a confounding factor in this setting because it had not been shown to be effective in prior studies [Gelbard *et al.* 1983].

Patient follow up was conducted at 4 weeks after the conclusion of treatment. Of the total 31

Table 1. Summary of clinical trials of intralesional CCH injection for the treatment of PD, including treatment regimens and efficacy data.

Study (Ref.)	Design	Patient population	Treatment (intralesional)	Efficacy
Gelbard et al. [1982] and Levine *et al.* [2014]	Phase I	CCH: 31	6 patients: 0.027–0.092 mg (mean 0.047 mg) CCH 25 patients: B-aminoproprionitrile fumberate + 0.101–0.281 mg (mean 0.156 mg) CCH	*Objective improvement* 20/31 (65%) *Plaque reduction* Small plaque: 50% of patients Moderate plaque: 75% of patients Large plaque: 65% of patients
Gelbard et al. [1993] and Desai and Hentz [2010]	Phase II: randomized double blind, placebo controlled	Total: 49 CCH: 22 Placebo:27	0.348 mg, 0.580 mg and 0.812 mg CCH	*Positive response* CCH: 8/22 (36%) Placebo: 1/27 (4%) $p = 0.007$
Jordan [2008] and Holzer and Holzer [2011]	Phase II: open label	CCH: 25		*Decreased penile curvature* 10/19 (53%) *Plaque reduction* 18/19 (95%)
Gelbard et al. [2012] and Kaplan [2011]	Phase IIb: randomized double blind, placebo controlled	Total: 147 CCH (total): 111 a. Modeling: 54 b. No modeling: 55 Placebo (total): 36 a. Modeling: 20 b. No modeling: 16	*Treatment cycle* Two 0.58 mg CCH injections 24–72 h apart Three treatment cycles in 6 weeks	*Mean reduction in penile curvature* CCH: 29.7% (–16.3° ± 14.6°) mean reduction of penile curvature Placebo: 11% (–5.4° ± 13.8°) mean reduction of penile curvature *Modeling* CCH: 32.4% (–17.5° ± 15.3°) decrease Placebo: 3% (0.6° ± 13.2°) decrease *No modeling* CCH: 27% (–15.0° ± 14.0°) decrease Placebo: 28% (–13.0° ± 10.7°)
Gelbard et al. [2013] and Levine *et al.* [2015]	Phase III: two identical randomized, double-blind, placebo-controlled studies	IMPRESS I Total: 417 CCH: 277 Placebo: 140 IMPRESS II Total: 415 CCH: 274 Placebo: 141	*Treatment cycle* Two 0.58 mg injections 24–72 h apart Four treatment cycles in 6-week intervals	*Mean reduction in penile curvature* CCH: 34% (–17.0° ± 14.8°) Placebo: 18% (–9.3° ± 13.6°)
Levine et al. [2015] and Hellstrom *et al.* [2006]	Phase III: open label	CCH: 347	*Treatment cycle* Two 0.58 mg injections 24–72 h apart Four treatment cycles in 6-week intervals	*Mean reduction in penile curvature* 34% (–18.3° ± 14.02°)

CCH, clostridium collagenase histolyticum; IMPRESS, investigation for maximal Peyronie's reduction efficacy and safety studies; PD, Peyronie's disease.

patients who underwent intralesional CCH injection therapy, 20 (65%) had objective improvement within 2 weeks; 16 patients experienced decreased penile curvature of 20–100% and the remaining four patients experienced near or complete disappearance of their penile plaques. Plaque deformity was reduced in 50% of patients with small or impalpable plaques, in 75% of the 12 patients with moderate plaques, and in 65% of the 13 patients with large plaques. Fourteen of the 31 patients in the study had reported painful erections, and 13 of these patients reported no longer having pain. Prior to treatment, four individuals reported not being able to have intercourse; following treatment, three of these patients regained the ability. Both patients with circumferential plaques, and only one of five total patients with decreased firmness of erection distal to the plaque had any improvement following injection therapy.

Gelbard and colleagues continued to investigate the efficacy of intralesional CCH injections for the treatment of PD in a follow-up, double-blind, placebo-controlled trial of 49 individuals [Gelbard *et al*. 1993]. Patients were grouped into three categories depending on the severity of PD, as indicated by penile curvature and plaque size. The three categories of disease severity were as follows: group 1: penile curvature up to 30° or a palpable plaque of less than 2 cm; group 2: 30–60° of curvature or a palpable plaque between 2 and 4 cm; and group 3: over 60° of curvature or a palpable plaque greater than 4 cm. Intralesional CCH injection dosing was 0.348 mg, 0.580 mg, and 0.812 mg in groups 1, 2, and 3, respectively.

At follow up, patients self-reported a positive response to treatment, which was then confirmed with plaque measurement or photographic confirmation of a reduction in penile curvature. The only patients who experienced a statistically significant positive treatment response were those in group 2, in which 4 of 11 patients treated with intralesional CCH injections were improved compared with placebo, in which 0 of 13 patients experienced improvement (36% *versus* 0%, $p = 0.03$). When the treatment group was analyzed as a whole for positive treatment response compared with placebo, a statistically significant difference was observed, with 8 of the 22 patients receiving treatment experiencing positive responses, compared with 1 of 27 individuals in the placebo group (36% *versus* 4%, $p = 0.007$).

Next, a phase II trial was conducted by Jordan in 2008 involving 25 patients, again to evaluate treatment response of PD to intralesional CCH injections [Jordan, 2008]. Study participants received injections for 7–10 days, and injections were repeated at 3 months. Follow-up assessment was performed at 3, 6, and 9 months post treatment. In this study, participants were said to have a positive response to treatment if a 25% decrease in penile curvature, as well as a 25% reduction in plaque size, was achieved. The greatest reduction in penile curvature and plaque size was observed at 3 months post treatment. Of 19 patients, 53% experienced a positive response to treatment as defined above in terms of decreased penile curvature, and 94% experienced decreased plaque size. Patients were asked 'How does your condition interfere with your ability to have a sex life?' and they responded that there was a significant improvement at all follow-up intervals. This study showed an overall 52% positive treatment response rate across a cohort of patients with varied severity of disease.

In 2012, a phase IIb clinical trial of 147 individuals were randomized into four groups, those receiving CCH injections or placebo, both with and without penile modeling [Gelbard *et al*. 2012]. One treatment cycle consisted of two intralesional injections, 0.58 mg each for those receiving CCH, administered 24–72 h apart. Patients received up to a maximum of three treatment cycles, spaced 6 weeks apart. If an individual was in a group receiving penile modeling, this therapy was given 24–72 h following the last injection of a treatment cycle. Outcome measures included final penile curvature, self-reported patient outcomes, and adverse reactions to therapy.

Patients in the treatment arm experienced a significantly greater mean reduction of penile curvature of 29.7% (–16.3° ± 14.6°) than patients in the placebo arm who experienced a mean reduction in penile curvature of 11% (–5.4 ± 13.8°; $p < 0.001$). This improvement was observed first at the 6-week time point, and continued until 36 weeks following initial treatment. Those patients receiving penile modeling in addition to CCH injection therapy experienced a significantly greater response to treatment, with an overall improvement of 32.4% in penile curvature (–17.5° ± 15.3°), compared with the placebo group with a 3% change in curvature (0.6° ± 13.2°; $p < 0.001$). Those men in the treatment

arm who did not undergo modeling saw an average decrease in penile curvature of 27% (–15.0° ± 14.0°), a reduction that does not vary significantly from that observed in placebo individuals of 28% (–13.0° ± 10.7°). Notably, patients receiving intralesional CCH injections demonstrated significant overall improvement in the symptom bother domain of the PDQ and International Index of Erectile Function (IIEF) sexual satisfaction score over the placebo group.

In 2013, the phase III trials IMPRESS I and II were initiated. The studies were identical prospective, large-scale, placebo-controlled, double-blind randomized controlled trials of 832 individuals combined [Gelbard *et al.* 2013]. Effects of CCH therapy were assessed over a period of 1 year in men from 64 sites in the United States and Australia. Primary outcome measures included change from baseline in penile curvature and symptom bother domain of the PDQ. Secondary outcome measures were changes in firmness of penile plaques, penile length, score on the IIEF overall satisfaction domain, percent of treatment responders, percent of composite responders, and change in penile pain and psychological/physical symptoms as measured by the PDQ. A composite responder was a subject with an improvement in penile curvature of at least 20.0% as well as a PDQ bother score improvement of at least 1, or a man who reported sexual activity who had previously reported no sexual activity at screening. In this study, one treatment cycle was defined as two intralesional CCH injections directed at the primary plaque at the location of maximal penile curvature, dosed at 0.58 mg each or placebo, and administered 24–72 h apart. Up to four treatment cycles were administered at 6-week intervals, continuing if penile curvature remained greater than 15°. Penile plaque modeling was performed on all patients at 24–72 h following the last injection of a treatment cycle; patients were also educated to self-perform penile modeling at home three times daily.

There was a statistically significant greater reduction in penile curvature in the group treated with intralesional CCH injections than those receiving placebo (34%, –17.0° ± 14.8° and 18%, –9.3° ± 13.6°, respectively; $p < 0.0001$). Additionally, symptom bother score on the PDQ questionnaire was significantly improved in those receiving CCH treatment compared with placebo. Penile plaque consistency was graded on a scale of 1 (nonpalpable) to 5 (hard); treatment group plaque consistency decreased by 0.8 ± 1.0, whereas placebo group plaque consistency decreased by 0.5 ± 0.9. In fact, all secondary outcome measures except penile length and the penile pain domain of the PDQ showed statistically significant improvements in CCH treatment *versus* placebo groups.

Most recently, an open-label, phase III clinical trial was conducted in 2015 by Levine and colleagues that looked at the same primary outcome measures of change in penile curvature and score on the symptom bother domain of the PDQ in 347 individuals [Levine *et al.* 2015]. Secondary outcome measures were change in IIEF overall satisfaction domain score, psychological and physical symptoms as measured by the PDQ, change in PD symptoms and effects on a global questionnaire, penile plaque consistency, penile length, and plasma AUX-1 and AUX-II levels. Similar to previous studies, a treatment cycle comprised two intralesional injections of CCH, dosed at 0.58 mg each, and administered 24–72 h apart. Modeling was also performed following the second injection in a treatment cycle, and up to four treatment cycles were given at 6-week intervals.

Decreased penile curvature was observed from the time of the first treatment cycle throughout 36 weeks. Patients experienced a mean decrease in penile curvature of 34% (−18.3° ± 14.02°). When patients were separated into categories by baseline curvature severity, the response to treatment was consistent with patients with 30–60° of curvature experiencing a 33% decrease in deformity, and of those with 61–90° of curvature experiencing a 37% improvement. Symptom bother domain score on the PDQ was significantly decreased at the 36-week time point compared with baseline, regardless of severity of baseline penile curvature (−3.3, 95% confidence interval 2.8–3.7). Secondary outcome measures also showed significant improvement with CCH treatment. Responses to a global assessment questionnaire administered at 24 and 36 weeks showed that 72% of treatment subjects felt they had a small but important improvement, moderate improvement or much improvement in their PD. Results from this study were robust, with 56% of patients achieving a decrease in penile curvature of at least 20%, and either a one point or greater decrease in the symptom bother domain of the PDQ or reestablishment of the ability to be sexually active.

Conclusion

Over the last three decades, CCH has emerged as a safe and effective pharmacologic treatment option for PD, and as an alternative to the more invasive surgical treatment. Previously, the drug had demonstrated applications in similar connective tissue diseases such as Dupuytren's contracture. Its well-studied profile has demonstrated the drug is safe and well tolerated, with adverse events that are typically mild to moderate, including pain, edema, and bruising, that resolve spontaneously with conservative management. CCH use has been documented through multiple clinical trials, including the two large, multicenter IMPRESS I and II trials, to result in significant decreases in penile curvature and plaque size when administered as multiple, spaced treatment cycles, and the greatest effect is observed when penile modeling is performed following treatment cycles. This therapy also improves the majority of PDQ symptom domain scores, indicating that psychological factors, and not only physical factors, are improved in patients with PD treated with CCH. Although CCH has been well studied up until this point, additional large-scale studies are needed to assess less well understood facets of treatment, including long-term side effects and lasting effect of treatment as well as the effectiveness of CCH in the setting of additional penile deformities such as loss of length, hourglass, and indentations.

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Conflict of interest statement

EJT, WW, and FAY report no conflict of interest in this work. WJGH was the primary investigator for the IMPRESS studies and is on the advisory board for Endo Pharmaceuticals.

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