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REVIEW

Role of collagenase clostridium histolyticum in Peyronie's disease

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Abstract: Peyronie's disease is a localized connective tissue disease characterized by an active, inflammatory phase and a stable, quiescent phase, with the eventual development of collagenous plaques within the tunica albuginea of the penis. Risk factors primarily associated with Peyronie's disease include Dupuytren's contracture, penile trauma, and family history. A variety of treatment strategies have been utilized, including oral and topical agents, electromotive drug administration, intralesional injections, extracorporeal shockwave therapy, penile traction, and surgery. However, most of these strategies are ineffective, with surgery being the only definitive treatment. Collagenase clostridium histolyticum is a newly US Food and Drug Administration-approved agent for intralesional injection. It is thought to downregulate many of the disease-related genes, cytokines, and growth factors and degrade collagen fibers. It also suppresses cell attachment, spreading, and proliferation. Collagenase clostridium histolyticum has been clinically proven to be a safe and effective therapeutic option, demonstrating decreases in penile curvature and plaque consistency, as well as increases in patient satisfaction. During clinical evaluation, the Peyronie's Disease Questionnaire was validated as an effective tool for assessing treatment outcomes.

Keywords: connective tissue disease, CCH, Xiaflex, Peyronie's Disease Questionnaire

Introduction

Peyronie's disease (PD) is a connective tissue disease characterized by a progressive fibroblastic proliferation of collagenous plaques of the tunica albuginea of the penis (Figure 1).[1] These plaques can result in various penile malformations, including curvature, indentation, narrowing, shortening, hourglass-like shape, and buckling erections.[2] It has been difficult to properly estimate the prevalence and incidence of this disease due to a wide range of values obtained through epidemiological studies. Studies have demonstrated values ranging from 0.3% to almost 7%.[3] Many physicians continue to postulate that the true prevalence is approximately 1%. However, recent studies consistently indicate that the prevalence is much higher. In a study of 534 men undergoing prostate cancer screening in the US, 8.9% were found to have objective evidence of PD.[4] Despite the uncertainty, it is safe to say that PD is more prevalent than once believed, and, due to many patients' unwillingness to seek medical treatment, the true value will likely continue to be underestimated.

There have been many proposed risk factors to explain the susceptibility and progression of PD, though some have been studied and validated more than others. One of the most prevalent risk factors is Dupuytren's contracture, with an estimated 30%–40% of PD patients also having this analogous fibrotic condition of

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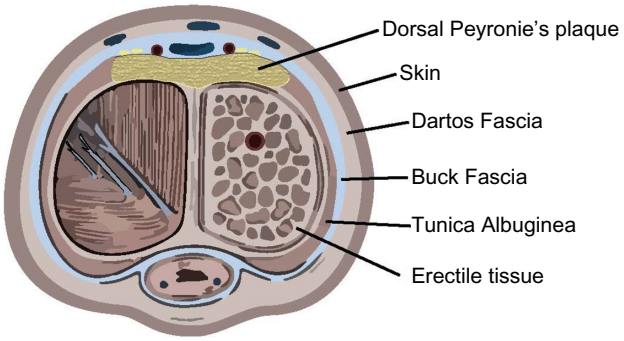

Figure 1 Cross-sectional view of a penis with a dorsally located plaque.

the hand.[5,6] Penile trauma is another condition classically associated with PD. One survey indicated that 40% of men diagnosed with PD reported some form of penile trauma while either erect or flaccid.[7] An inheritable component has also been documented in 2% of patients.[8] In addition, use of β-adrenergic blockers, plantar fascial contractures, tympanosclerosis, urethral instrumentation, radical prostatectomy, and gout are all considered to be risk factors for the development of PD, although the evidence for these is weaker.[9] In terms of progression, evidence suggests that patients with diabetes mellitus have an increased risk of PD. One study demonstrated that men with both PD and diabetes mellitus had a more severe penile curvature, an increased rate of erectile dysfunction (ED), and significantly higher rates of arterial insufficiency and mixed vascular disease than in those men with PD alone.[10] Another study reported evidence suggesting that decreased testosterone levels may produce more severe PD symptoms.[11]

The precise pathophysiologic mechanism of PD is also controversial, despite being first described in 1743. Simply stated, it is a disorder of wound healing and excessive collagen deposition resulting from some combination of chronic microtrauma versus acute macrotrauma, the previously mentioned risk factors, and genetic predisposition. Exactly why microtrauma causes an excessive inflammatory response in some individuals remains poorly understood. From a histological standpoint, the mechanism behind the collagen deposition of PD is fairly well characterized. First, trauma to the tunica albuginea causes the release and deposition of fibrin. Fibrin, in turn, causes an increase in transforming growth factor-β1 (TGF-β1).[12] Acting as a profibrotic cytokine, TGF-β1 stimulates the deposition of collagen by fibroblasts and myofibroblasts. In addition, it inhibits the breakdown of connective tissue by collagenase. TGF-β1 also triggers the formation of reactive oxygen species and inhibits the effects of nitric oxide. Further downstream, reactive oxygen species specifically stimulate the deposition of type III collagen in an unorganized fashion, promoting calcification.[13]

The progression of PD is divided into two phases: the active, inflammatory phase and the stable, quiescent phase. The active phase is the initial phase and is characterized by painful erections, an evolving plaque, and progressive penile curvature.[14] This phase lasts anywhere from 6 months to 2 years, with reports indicating that 94% of men experience plaque stabilization and resolution of coital pain within 18 months from symptom onset.[4] The quiescent phase is characterized by stability of the penile deformity, resolution of penile pain, and, in some, the onset of ED. An analysis of the natural progression of PD without treatment revealed that, at follow-up, the penile curvature improved in 12% of patients, remained stable in 40%, and worsened in 48%.[15] Another more recent study found that penile pain, deformity, and plaque size increase over time in the majority of patients with no treatment. Furthermore, this progression correlated with a patient's risk of developing fibrosis.[16] Due to the fact that progression of the disease occurs in a significant number of patients, any progression should be evaluated and treated.

In a PD patient evaluation, it is important to perform a detailed history, psychosexual evaluation, and physical examination. A history may elicit previous trauma as well as medications and other disease processes associated with PD. A psychosexual evaluation is of critical importance because PD has an enormous impact on the psychological well-being of the patient. One study found that 48% of patients diagnosed with PD had depression, with 26% classified as moderate, 21% classified as severe, and 1% unspecified.[17] Identifying and treating this psychological instability is an important component in the treatment of the PD patient. In performing a physical examination, the plaque should be adequately characterized by putting the penis on stretch and defining its size, location, and consistency. The degree of curvature is also evaluated, often in conjunction with a vascular study, by producing a pharmacologic erection and performing a duplex Doppler ultrasound.[18]

Current treatment strategies

PD has proven to be difficult to treat, and the search for an optimal treatment continues. Furthermore, many of the initial studies to evaluate treatment modalities were poorly designed.[19] Nevertheless, there is a diverse array of therapies employed, including oral systemic agents, topical agents, electromotive drug administration (EMDA), intralesional injections, extracorporeal shockwave therapy, penile traction therapy, and surgery.

Oral, systemic agents that have been evaluated include vitamin E, colchicine, potassium para-aminobenzoate, tamoxifen, carnitine, and pentoxyfilline. Of these medications, only para-aminobenzoate and pentoxyfilline have shown some clinical efficacy. Para-aminobenzoate decreases plaque size and prevents disease progression by inhibiting fibroblast glycosaminoglycan secretion.[20,21] However, it is expensive and causes significant gastrointestinal side effects, and, as such, is rarely prescribed by physicians. Pentoxyfilline, a nonspecific phosphodiesterase inhibitor that has anti-inflammatory and antifibrogenic properties, decreases plaque size as well as the curvature of the penis.[22] Vitamin E, a free radical scavenger, has been shown to decrease pain and, thus, is often initially given while patients are awaiting disease stabilization, despite no clinically proven efficacy.[13,23–26]

Topical agents, often used in conjunction with EMDA, have likewise been controversial in their use as PD treatments. Topical agents that have been described include verapamil and dexamethasone. During EMDA, a current is passed over the penis, repelling positively charged verapamil ions and dexamethasone (phosphate) into underlying diseased tissues. Verapamil, evaluated in several initial, open-label studies, provided clinical improvement in 62%–90% of patients, as provided by history and ultrasonography.[13] However, a double-blinded, placebo-controlled trial comparing verapamil to saline in EMDA showed no statistically significant change in penile curvature.[27] Use of corticosteroids has also been discouraged due to tissue atrophy, skin thinning, and immune suppression.[20] With conflicting evidence, there have been few recent clinical trials assessing the efficacy of verapamil administered with EMDA. One more recent trial, however, showed that while it is a safe and reliable treatment to resolve painful erections in the acute phase of PD, its efficacy in solving penile curvature and ED is limited.[28]

Intralesional injections have consistently proven to be the most effective medical therapy, decreasing plaque size, penile curvature, and in some instances, pain (Figure 2). The use of interferon α-2b, verapamil, and more recently, collagenase clostridium histolyticum (CCH) have shown variable degrees of efficacy. In multiple trials, interferon α-2b demonstrated statistically significant improvements in penile curvature, plaque size, and plaque density in comparison

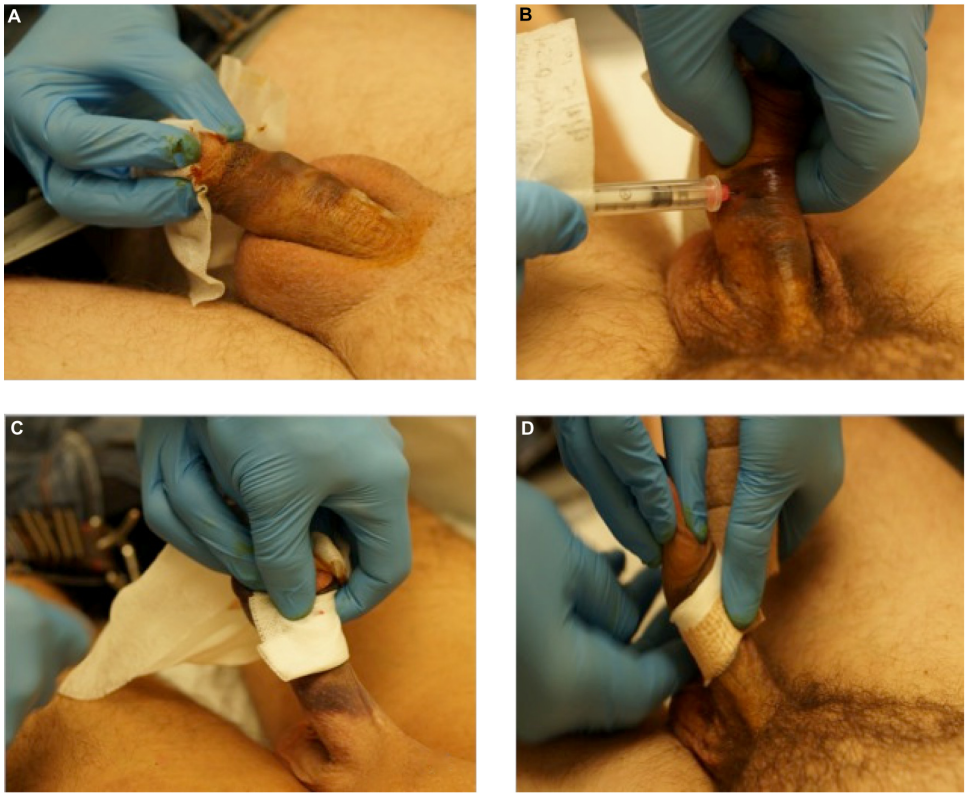

Figure 2 Administering CCH injections for Peyronie's Disease with evident bruising as a common side effect.
Notes: (**A**) The penis is put on stretch and the location, size, and consistency of the plaque is inspected. (**B**) After application of a local anesthetic, 0.58 mg of CCH is injected into the plaque, with the needle entering from the side. (**C**) The penis is wrapped with sterile gauze immediately after injection. (**D**) The gauze is wrapped tightly in order to prevent the development of a hematoma.
Abbreviation: CCH, collagenase clostridium histolyticum.

to placebo.[29,30] Intralesional verapamil has likewise been shown to decrease plaque size, improve erectile function, and decrease penile curvature.[31] When combining intralesional verapamil with its topical form, antioxidants, and a nonsteroidal anti-inflammatory drug, improvements in curvature and plaque volume occurred in patients at both 6 months and 18 months.[32] The use of CCH (XIAFLEX®, Auxilium Pharmaceuticals, Inc., Chesterbrook, PA, USA) will be comprehensively discussed in the other sections of this review.[33]

It was initially proposed that extracorporeal shockwave therapy would decrease plaque size, increase vascularity, and increase macrophage activity. Studies have, however, been inconclusive thus far as to its efficacy, with some data reporting decreased pain and improved erectile function with no changes in plaque size or penile curvature.[34]

Surgery is the most invasive line of treatment, but is still considered the gold-standard therapy for PD. Of note, the use of surgical procedures is restricted to PD cases that have remained stable for at least 12 months. Surgical options include tunical plication, plaque excision/incision and grafting, and penile prosthesis implantation with or without ancillary procedures such as manual modeling, plication, and grafting. The procedure chosen depends on several factors, including degree, location, extent of penile curvature, and baseline erectile function. Tunical plication is the preferred method for men with adequate rigidity and curvature $<60°$ without narrowing. Men who have more severe deformity and hourglass deformity but strong erections should be considered for partial excision/incision and grafting. Finally, for those men who have inadequate erectile function despite oral phosphodiesterase-5 inhibitors, penile prosthesis is the best option.[35]

Collagenase clostridium histolyticum

Mechanism of action

The enzyme CCH was first isolated in 1953 and later introduced in 1996 as a novel therapeutic agent to treat Dupuytren's contracture.[36,37] There are a total of seven different collagenases that have been isolated and divided into two classes based on protein domain, substrate specificity, and gene of origin. These two classes of enzymes attack triple-helical type I and III collagens using a class-specific mechanism. Type I enzymes, labeled AUX-I by the manufacturers of CCH, hydrolyze N- and C-terminal–end triple-helical peptide domains. In contrast, class II enzymes, or AUX-II, begin hydrolyzing internal peptide domains with less specificity but higher affinity.[38–40] On a cellular level, CCH downregulates many of the extracellular matrix-associated genes, cytokines, and growth factors that are overexpressed during the development of PD plaques. An in vivo study found that administration of CCH not only destroyed collagen fibers but also suppressed cell attachment, spreading, and proliferation.[34] CCH administration was also associated with suppressed expression of alpha-smooth muscle actin, TGF-β1, fibronectin, and desmin, and it induced membrane leakage and decreased metabolic activity within fibroblasts. Altogether, this enzyme both downregulates the abnormal expression of type I and III collagens and destroys the pathological collagen plaques that cause the curvature of PD. It does not attack collagen type IV except at the highest dose of CCH and at longer incubation times. This selectivity is important because collagen type IV is a major structural component present in the connective tissues that surround arteries, large veins, and nerves.[41] Because type IV is largely spared with CCH use, there is preferential destruction of diseased tissue, with a smaller risk of significant damage to healthy tissue.

Pharmacology

In evaluating the pharmacokinetic profile of CCH in PD treatment, researchers administered two intralesional injections 24 hours apart at a dose of 0.58 mg and measured the plasma levels of AUX-I and AUX-II in subjects. The maximal plasma concentrations of AUX-I and AUX-II were <29 ng/mL and <71 ng/mL, respectively, and were observed within 10 minutes after the injection. All plasma levels were below quantifiable levels within 30 minutes of injection. Furthermore, 3 days after injection, no subject had quantifiable plasma levels 15 minutes after modeling of the plaque.[42] In an animal model, when administered intravenously in rats at exposure levels up to 11 times the maximum recommended human dose, CCH did not impair fertility or early embryonic development. There was also no observed systemic toxicity when administered to rats and dogs subcutaneously, nor during intrapenile injection of dogs.[33] There have been no studies evaluating CCH's effect on metabolizing enzyme pathways because it is not a substrate for cytochrome P450 enzymes and produces no active metabolites. In the initial clinical trials, CCH was administered in doses reported in active biofactor units. The conversion factor for CCH is 10,000 active biofactor units equals 0.58 mg.[43] For convenience, all doses will be reported in milligrams.

Clinical efficacy: penile curvature and deformity

Phase I clinical testing of CCH began in 1985 by Gelbard et al.[44] In his pilot study, 31 patients were treated with

varying doses of CCH and then evaluated for changes in plaque size, penile curvature, and pain. As part of the protocol, six patients received a single intralesional injection of CCH on 3 consecutive days, with total doses ranging from 0.027 mg to 0.093 mg (mean 0.047 mg). The other 25 patients received a combination of CCH and daily beta-aminopropionitrile, with the CCH dose ranging from 0.101 mg to 0.281 mg total (mean 0.156 mg). All received follow-up evaluation 4 weeks after the treatment. The addition of beta-aminopropionitrile, an inhibitor of lysyl oxidase thought to increase collagen laxity, was not believed to be a confounding variable due to its lack of efficacy in previous trials.

Of the 31 patients treated intralesionally, 20 (65%) had objective improvement, usually within 2 weeks. Plaques disappeared or were significantly altered in configuration in four patients, and penile curvature decreased 20%–100% in the remaining 16. Relief of deformity occurred in 50% of the 6 patients with small or impalpable plaques, in 75% of 12 patients with moderate lesions, and in 65% of the 13 patients with large lesions. Of the 14 patients who entered the study reporting pain, 13 reported complete relief after treatment. Three of the four men who were unable to have intercourse at the initiation of the trial regained the ability. Unfortunately, only one of the five patients with decreased erectile rigidity distal to the plaque – and neither of the two patients with circumferential plaques – showed improvement after therapy.

As a follow-up to their initial trial, Gelbard et al investigated the effects of CCH on plaque size and penile deformity in 49 men with PD in a prospectively randomized, placebo-controlled, double-blind study.[45] Patients were separated into three categories based on degree of curvature and/or plaque size: Category 1 had a curvature of ≤30° and/or plaque size <2 cm; Category 2 had a curvature between 30° and 60° and/or plaque size between 2 and 4 cm; Category 3 had a curvature >60° and/or plaque size >4 cm. Patients received 0.348 mg, 0.580 mg, or 0.812 mg of CCH, depending on if they were in Category 1, 2, or 3, respectively, and were followed up at 1 week, 1 month, and 3 months. A positive response was defined as patient-reported improvement that was confirmed with documented plaque measurements or photography of erection.

A positive response was only found to be statistically significant in Category 2 with 4 of the 11 (36%) patients in the treatment group experiencing improvement, compared to none of the 13 patients (0%) in the placebo group (P=0.03). The treatment groups as a whole were then compared to the placebo groups. In total, 8 of the 22 (36%) patients in the treatment groups experienced a positive response, while only 1 out of 27 (4%) did so in the placebo groups, proving to be statistically significant in this study (P<0.007).

In a Phase IIb trial, 147 patients were randomized into four groups to receive CCH or placebo, with or without penile plaque modeling.[46] During each treatment cycle, two intralesional injections of CCH (0.58 mg) or placebo were given with an interval of 24–72 hours between the injections. This regimen was repeated after 6 weeks for up to three treatment cycles. Between 24 and 72 hours after the second injection of each treatment cycle, subjects randomized to modeling underwent gradual, gentle stretching of the flaccid penis in the opposite direction of the curvature. Penile curvatures, patient-reported outcomes, and adverse events were then assessed.

The mean penile curvature at baseline for patients randomized to the CCH group was 54.4°±15.1°, while that of the placebo group was 50.6°±15.1°. A mean change in penile curvature of −16.3°±14.6° was observed for the CCH treatment group, demonstrating a mean improvement of 29.7% per patient. This was a statistically significant improvement compared with the mean change of −5.4°±13.8° for placebo, an 11% improvement per patient (P<0.001). This decrease in penile curvature was observed as early as week 6 of treatment and continued through week 36. Furthermore, when analyzing the efficacy of penile modeling, patients who underwent the procedure showed a mean change of −17.5°±15.3° in curvature for CCH. This was an improvement of 32.4%, proving to be significant in contrast to the placebo group, which experienced a mean change of 0.6°±13.2° for placebo, a worsening of 2.5% (P<0.001). Patients without modeling experienced a mean change of −15.0°±14.0° when treated with CCH, an improvement of 27.1%. This did not statistically significantly differ from mean change −13.0°±10.7° for placebo, an improvement of 27.9% (P=0.9).

These promising results led to two Phase III trials for CCH, dubbed Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies I and II (IMPRESS I and II).[47] IMPRESS I and II were designed as large, identical, prospective, 1-year, double-blinded, randomized, placebo-controlled studies that enrolled men from 64 sites across the United States and Australia. Both studies were designed to assess for improvement in the co-primary efficacy endpoints, percent improvements from baseline in penile curvature, and change from baseline in the PD symptom bother domain. As secondary endpoints, researchers evaluated changes in penile plaque consistency, penile length, penile pain domain, and the International Index of Erectile Function (IIEF) overall

satisfaction domain. Further secondary endpoints included the proportion of treatment responders, the decrease in the severity of PD psychological and physical symptoms, and the percent of composite responders. As part of the protocol, each treatment cycle included two injections of CCH (0.58 mg) or placebo, directly injected into the primary plaque at the point of maximal penile curvature with an interval of approximately 24–72 hours between each injection. After 24–72 hours following the second injection of each treatment cycle, patients underwent penile plaque modeling performed by the investigator. Patients were also instructed to perform home penile modeling three times per day during the course of the study. The treatment cycle was repeated after 6 weeks for up to four treatment cycles. If the penile curvature abnormality was reduced to $<15°$, or the investigator determined further treatment was not clinically indicated, future cycles were not administered.

The mean penile curvature at baseline for IMPRESS I and II was 50.1°±14.4° and 49.3°±14° in men on CCH and placebo, respectively. Patients treated with CCH showed a mean change per subject of −17.0°±14.8°, equivalent to a mean improvement of 34.0%. Patients treated with placebo showed a mean change per subject of −9.3°±13.6°, equivalent to an 18.2% improvement. The improvement seen in the treatment group was statistically significant to that of the placebo group ($P<0.0001$). The plaque consistency, rated on a scale of 1–5, ranging from nonpalpable to hard, decreased by 0.8±1.0 points in the CCH group, in comparison to a decrease of 0.5±0.9 in the placebo group (Table 1).

Safety and tolerability

In the initial experiment by Gelbard et al in 1985, the injection of CCH was tolerated well. Two of the 31 patients reported pain at the injection site, while 21 experienced ecchymosis.[44] No patients reported numbness in the glans or referred pain to other regions of the body. There was one incidence of corporeal rupture that occurred during intercourse 2 weeks after treatment. Interestingly enough, after allowing time for his penis to heal, the patient reported straighter erections than before treatment, suggesting that the diseased plaque, disrupted by the effect of CCH, was torn during the rupture. In the 1993 follow-up study, Gelbard et al found that none of the 49 patients had severe, adverse responses or allergic reactions.[45] All patients reported tenderness at the injection site, but this finding was observed in those receiving placebo as frequently as those receiving CCH. There was one incidence of a small tear in the tunica 3 weeks following an injection, but the injury resolved after conservative treatment.

In the Phase IIb trial consisting of 147 patients, the investigator evaluated the most common adverse events, that is, those that developed in five or more patients.[46] Injection site bruising, edema, and pain were all common in those patients receiving CCH therapy, occurring in 86.5%, 45%, and 52.3% of the patients, respectively. This proved to be statistically significant in comparison to the placebo group, with 44.4%, 0%, and 11.1% of the patients reporting bruising, edema, and pain, respectively ($P<0.001$). Other nonsignificant adverse events included contusion (14.4%), ED (4.5%), painful erection (4.5%), penile edema (9.9%), and penile pain (9.9%). Despite the adverse events, only two patients in the CCH group discontinued therapy prematurely due to injection site bruising, edema, and rash. In addition, by the end of the trial at 36 weeks, all the patients had developed antidrug antibodies to AUX-I and AUX-II. Despite this drug-induced immune response, there were no systemic immunological events reported.

In the Phase III trials, IMPRESS I and II, both CCH- and placebo-treated groups tolerated the injections well, as in the previous Phase I and II trials.[47] The maximum possible number of injections was administered to 434 of 551 CCH-treated men (78.0%) and 247 of 281 placebo-treated men (87.9%). Treatment-related adverse events were reported in 464 men (84.2%) treated with CCH, compared to 102 men receiving placebo (36.3%). The most common adverse event reported, occurring in 80% of patients, was penile ecchymosis, which included injection site hematoma. Penile swelling and pain were also very common adverse events, occurring 55% and 45.4% of the time, respectively. As assessed by the investigators, adverse events were typically mild or moderate and 3,200 of 4,049 (approximately 79.0%) resolved without intervention within 14 days. Six men experienced what was considered serious, treatment-related adverse events. Three of these men suffered a corporeal rupture, all of which were successfully repaired with surgery. The other three serious adverse events were penile hematomas, one of which was successfully surgically repaired. Of the other two hematomas, one resolved without treatment and the other resolved after aspiration. By the end of the first cycle of CCH, 404 (75%) and 288 (53.4%) of 539 CCH-treated men had positive AUX-I and AUX-II antidrug antibodies, respectively. By the end of the trial at 1 year, 482 of 486 (99.2%) and 479 of 487 (98.4%) CCH-treated men had developed the antibodies to AUX-I and -II, respectively. As in the Phase IIb trial, no systemic immunological events were reported.

Table 1 A table summarizing the clinical trials and efficacy of CCH at reducing penile curvature and symptom bother domain

Clinical trial	Patient population	Dose	Results	Reference
Phase I	31 patients Mean age: 55 years	6 Patients: CCH 0.027 mg –0.093 mg (mean: 0.047 mg) 25 Patients: β-aminopropionitrile + CCH 0.101 mg–0.281 mg (mean 0.156 mg)	20/31 (65%) reported objective decrease in curvature	Gelbard et al[42]
Phase I	49 patients 22 – Treatment 27 – Placebo Eligibility: diagnosis of PD, stable or progressive for at least 3 months Category 1: curvature of ≤30° and/or plaque size <2 cm Category 2: curvature 30°–60° and/or plaque size between 2 and 4 cm Category 3: curvature >60° and/or plaque size >4 cm	Category 1: CCH 0.348 mg Category 2: CCH 0.580 mg Category 3: CCH 0.812 mg	Positive response Category 1: 3/3 – Treatment, 1/4 – Placebo (normal sterile saline) Category 2: 4/11 – Treatment, 0/13 – Placebo (P=0.03) Category 3: 1/8 – Treatment, 0/10 – Placebo (normal sterile saline)	Gelbard et al[43]
Phase II	147 patients 111 – Treatment 36 – Placebo Age: 45–64 years Eligibility: diagnosis of PD for ≥6 months, in a stable relationship for ≥3 months before screening, penile curvature of ≥30° and ≤90°	3 treatment cycles, 6 weeks apart, 2 injections per cycle, CCH 0.58 mg per injection	Overall mean change in curvature: −16.3°±14.6° – Treatment, −5.4°±13.8° – Placebo (P<0.001) Change in curvature: With modeling: −17.5°±15.3° – Treatment, 0.6°±13.2° – Placebo Without modeling: −15.0°±14.0° – Treatment −13.0°±10.7° – Placebo	Gelbard et al[44]
Phase III: IMPRESS I and IMPRESS II	IMPRESS I and II 832 patients 551 – Treatment 281 – Placebo Age: 28–81 years Eligibility: diagnosis of PD for ≥12 months and a stable disease before the first dose of CCH, in a stable relationship for ≥3 months before screening, penile curvature of ≥30° and ≤90°	4 cycles, 6 weeks apart, 2 injections per cycle, 0.58 mg per injection	*Overall mean change in curvature: −17.0°±14.8° – Treatment −9.3°±13.6° – Control *Overall mean change in PD symptom bother domain −2.8±3.8 – Treatment −1.8±3.5 – Placebo	Gelbard et al[45]

Note: *Statistical significance (P<0.05).
Abbreviations: CCH, clostridium collagenase histolyticum; IMPRESS, Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies; PD, Peyronie's disease.

Patient satisfaction

Due to the difficulty that clinicians have had in effectively treating the physical deformities of PD, the psychological effects attributed to the disease have, in the past, not been properly evaluated. As much as the collagenous plaques of PD cause physical deformity, they also can lead to severe psychosexual distress that impacts a patient's sexual self-image, sexual function, and interpersonal relationships. This is evident in prior studies showing that 81% of patients report emotional difficulties and 54% report relationship problems due to PD.[17,48]

More recently, Phase II and III studies have used questionnaires to effectively assess this definite psychological impact. The PD Patient-Reported Outcomes and IIEF questionnaires were used in the Phase IIb study to assess the impact of PD on patients' quality of life and erectile function.[46] The PD Patient-Reported Outcomes questions are based on an assessment of intercourse discomfort, penile pain, and PD symptom bother. The IIEF questionnaire is based on erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall sexual satisfaction.[49] Results from this study demonstrated that CCH-treated patients with penile modeling had a significantly better score on the PD symptom bother domain than those on placebo and modeling (P=0.004), with a decrease of 3.6 points in comparison

to a decrease of 0.1. There were no statistically significant differences when comparing CCH and placebo for improvements in intercourse discomfort, penile pain, or IIEF score.

In the IMPRESS I and II trials, the Peyronie's Disease Questionnaire (PDQ), a modified version of the PD Patient-Reported Outcomes used in the Phase IIb trial, was used to evaluate patient satisfaction. This questionnaire is a 15-question survey composed of three domains, including psychological and physical symptoms, penile pain, and symptom bother. It is limited by the fact that completion is dependent on having had vaginal intercourse within the previous 3 months. Serving as the other primary efficacy endpoint, the mean change in the PD symptom bother domain score was significantly improved in the CCH group compared to the placebo group. There was a decrease in the CCH group score of 2.8±3.8 points in comparison to a decrease in placebo of 1.8±3.5 (P=0.0037). When combining the data from both studies, an analysis showed that all the secondary endpoints, except for penile length and pain, showed statistically significant improvements. The percent of treatment responders, defined as patients with a global score improvement of at least 1 point, was statistically significant in the CCH group at 60.8%, in comparison to the placebo group at 29.5% ($P<0.0001$). The PDQ psychological and physical symptoms score, evaluated using the PDQ, decreased by 2.9±5.0 in the CCH group versus 1.3±4.6 in the placebo group (P=0.0021). Patients treated with CCH demonstrated increased IIEF scores of 1±2.4 in comparison to placebo increases of 0.4±2.4 (P=0.0189). The percent of composite responders, defined as men with ≥20.0% improvement in penile curvature plus an improvement in the PDQ PD bother score of ≥1 or a change from reporting no sexual activity at screening to reporting sexual activity, was reported as 46.6% in the CCH group and 28% in the placebo group at 52 weeks.

The PDQ was then validated using psychometric analyses to evaluate the data from IMPRESS I and II.[50] Investigators used the three PDQ domain scores, IIEF scores, objective penile curvature measures, and patient-reported PD symptom severity to determine if this questionnaire was a valuable tool in assessing treatment outcomes for PD. As part of their psychometric analysis, investigators initially used confirmatory factor analysis to determine if the PDQ adequately reflected their understanding of how to measure the psychological effects of the disease. Confirmatory factor analysis "goodness of fit" models included the Confirmatory Factor Index, Root Mean Square Error of Approximation, and Tucker-Lewis Index. A good fit model was defined by Confirmatory Factor Index and Tucker-Lewis Index as >0.9, and Root Mean Square Error of Approximation <0.08. The models showed that all three PDQ domains had adequate to good fit with observed data. To measure the internal consistency, defined as the ability of numerical scale-based questions to produce comparable results, investigators used Cronbach's α. They showed that in all three subset domains, the questions provided such consistency.

Conclusion

Intralesional injection of CCH for the treatment of PD is a fairly recent innovation that seeks to bridge the gap in efficacy between minimally invasive therapies such as with interferon or verapamil, and established invasive surgical therapies. CCH has previously been used to great effect in pathogenically similar disease processes such as Dupuytren's contracture and appears to be well tolerated. The results of the recent multi-institutional IMPRESS trial suggest that, in carefully selected patients, moderate improvement in Peyronie's curvature is possible with a series of CCH injections. As larger studies with long-term follow-ups become available, keen attention should be paid to treatment durability, prevalence of long-term adverse effects, and continued subjective assessment using validated instruments such as the PDQ. These quantities will help to determine how the intralesional CCH modality fits into the urologist's armamentarium for treating quiescent PD.

Disclosure

The authors report no conflicts of interest in this work.

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