Collagenase clostridium histolyticum: a novel nonsurgical option for the treatment of Peyronie's disease

Commercially available collagenase clostridium histolyticum (CCH) comprises a mixture of clostridial type-I/II collagenase enzymes, which enzymatically destroy collagen deposits. CCH is currently approved in the USA, EU and Canada for the treatment of Dupuytren's contracture with a palpable cord in the hands of adult patients. Intralesional injection of CCH has demonstrated safety and efficacy in the treatment of Peyronie's disease (PD) in Phase I–III clinical trials. Improvement of penile curvature deformity and psychological symptoms (degree of patient bother associated with PD) has been achieved among patients with PD. CCH is safe and well tolerated, with adverse events localized to the injection site. This article reviews the potential mechanism of action and summarizes the clinical experience with CCH in patients with PD.

KEYWORDS: collagen plaques ■ collagenase ■ curvature deformity ■ nonsurgical therapy ■ Peyronie's disease ■ XIAFLEX® ■ XIAPEX®

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Peyronie's disease (PD) is a localized connective tissue disorder characterized by the formation of fibrous, inelastic, predominantly collagenous plaques of the tunica albuginea of the penis. Associated clinical findings include any combination of penile deformity (bending, narrowing, shortening, development of a hinge effect), pain and/or psychological disturbance [1,2]. Anatomic and physiologic abnormalities associated with PD may result in progressive impairments in erectile function due to penile curvature, veno–occlusive dysfunction, pain or psychological factors, among others [3–6].

The reported prevalence of PD among adults in the USA varies widely, and ranges from 0.5–7.1% of the general population, to 8.1–20.3% of patients with comorbid conditions, including diabetes mellitus (DM), erectile dysfunction and prior prostatectomy [7–11]. Given the nature of PD, estimated prevalence rates may be underestimated due to patients' reluctance in approaching physicians for diagnosis and treatment [2,12].

PD is a progressive disorder in 30.2–48.0% of patients, with contemporary reports demonstrating low rates of spontaneous improvement (3.2–12.0%) [5,13]. Risk factors for early disease progression include younger age of onset of PD (<50 years) and the presence of comorbid systemic vascular disease, such as DM [14]. It has been demonstrated that DM is associated with a more severe mean degree of penile curvature deformity (45.2° vs 30.2°) and with a greater frequency of penile curvatures (>60°) compared with men who do not have DM (27.1 vs 5.5%) [15]. Likewise in one report, patients with testosterone deficiency, which is hypothesized to interfere with wound healing, had more severe curvature deformity compared with patients with normal testosterone levels (54.3° vs 37.1°) [16].

Although PD has been a defined condition for over 200 years, the pathophysiology remains poorly understood, and is believed to result from repeated micro/macro trauma to the penis in susceptible individuals with congenital abnormalities in wound healing [17–19]. PD may have similar pathophysiologic mechanisms to Dupuytren's contracture (DC), with both conditions being characterized by excessive collagen deposition and frequently coexisting [20–22]. From a histologic perspective, PD is associated with disorganized elastic tissue fibers, inflammation and irregular deposition of collagen fibrils, with types I and III collagen predominantly expressed [23–26]. TGF-β1 may play an important role in the development of PD plaques through induction of collagen production by fibroblasts/myofibroblasts [18,27,28]. Myofibroblasts deposit collagen in response to factors, such as TGF-β1, and are frequently found in conditions associated with fibrosis and abnormal wound healing [18]. *In vitro* studies in primary cultured human PD fibroblasts demonstrated antifibrotic effects through selective inhibition of ALK5, a TGF-β1 receptor specifically involved in TGF-β activation [29].

Clinically, PD is characterized as occurring in two phases: acute and chronic [5,30,31]. The acute or inflammatory phase occurs in the

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first 6–18 months of the disease, during which patients may frequently note symptoms of penile pain, progressive penile curvature and/or plaque formation. During the chronic phase, the penile plaques and deformity stabilize, with typical resolution of the penile pain [5]. Calcification of PD plaque(s) may occur in a minority of patients and results in a more challenging treatment condition [18,32].

In addition to physical and sexual effects, PD has an enormous impact on the psychological wellbeing of patients, as evidenced by high rates of depression, anger and decreased self-esteem [33,34]. Nelson *et al.* reported a high rate of clinical depression in men with PD and indicated that most men do not adjust to their diagnosis [33]. The study demonstrated that 48% of PD patients are clinically depressed (26% classified as moderate and 21% classified with severe depressive symptoms). A further subset analysis demonstrated that the level of depression does not vary significantly with symptom duration. Men with a 6–12-month duration of PD since diagnosis had similar levels of depression as men whose symptoms began >18 months prior to the study (54 vs 56%, respectively). Penile shortening and being single are predictive factors for depression in men with PD, as evidenced by a higher rate of depression in this cohort. Men with PD also report high rates of emotional problems (81%) and relationship difficulties (54%), with common psychosexual concerns including physical appearance, body image, self-esteem and masculinity [34,35]. In order to adequately quantify the psychological symptoms associated with PD, the PD Questionnaire (PDQ) was developed and validated in two identical, randomized, placebo-controlled trials of men with PD [36,37].

Brief overview of PD therapies

Currently available therapies for PD include topical agents, oral systemic agents, electromotive drug administration, iontophoresis, extracorporeal shockwave therapy (ESWT), traction therapy, intralesional injections and surgical correction.

Historically, clinical trials performed with the majority of nonsurgical therapies have shown inconsistent or ineffective results [31,38]. Available oral and topical therapies have failed to consistently demonstrate benefits with regards to penile deformity, with the 2010 International Consultation on Sexual Medicine guidelines suggesting that there is insufficient evidence to recommend any oral therapy for the treatment of penile deformity [31]. Topical therapy with verapamil and dexamethasone administered via electromotive iontophoresis has demonstrated improvements in curvature in controlled trials, although data are limited, with some authors suggesting no benefits on improving curvature or plaque size [31,39,40]. Penile traction therapy has additionally demonstrated some benefits on curvature and penile length in limited trials, although this remains controversial with additional study required [41]. Adverse effects (AEs) of oral therapies vary depending on agent, dose and duration of therapy, with and topical therapies resulting predominantly in local irritation, erythema, ecchymosis or hematoma.

Intralesional injection therapies with verapamil, interferon α-2b or collagenase clostridium histolyticum (CCH) have shown some degree of efficacy in improving penile curvature, reducing plaque size and density, and reducing penile pain, with randomized controlled trials confirming benefits with interferon and CCH [37,42,43]. AEs associated with intralesional therapies include pain, flu-like symptoms (interferon), ecchymosis or hematoma, among others. To date, currently available intralesional treatments are utilized in an off-label fashion and are not approved by the US FDA for the treatment of PD in the USA.

Surgery is currently considered the gold-standard therapy for the correction of penile curvature and includes penile plication, incision with or without grafting and placement of a penile prosthesis [44]. Given the progressive nature of PD, surgery is performed in patients with stable disease characteristics and is frequently reserved for those with deformities precluding sexual activity [31]. Surgical correction is associated with AEs including penile shortening, loss of sensation, recurrent curvature deformity and decreased erectile function [45,46]. Given the invasive nature of surgery and potential AEs, there remains a significant role for alternative, less invasive therapies.

Collagenase clostridium histolyticum

The enzyme CCH was first isolated in 1953 and has been extensively studied ever since [47]. CCH emerged as a potential therapeutic option for the treatment of DC in 1996, with the potential advantage of target specificity [48]. Currently, CCH (XIAFLEX® [Auxilium Pharmaceuticals Inc., PA, USA] in the USA and Canada, and XIAPEX® [Pfizer Inc., NY, USA] in the EU) is approved in the USA, EU and Canada for the treatment of adult patients with DC with

a palpable cord [49]. CCH is currently undergoing FDA review for the treatment of PD, and has demonstrated safety and efficacy as a nonsurgical treatment option for men with PD in one Phase II and two Phase III clinical studies [36,50]. The purpose of the current review is to evaluate the biomolecular properties of CCH, as well as the existing clinical evidence regarding its efficacy and safety in the treatment of PD.

Chemistry

The only commercially available CCH comprises a fixed ratio mixture of clostridial type I collagenase and clostridial type II collagenase (named AUX-I and AUX-II [Auxilium Pharmaceuticals, Inc., PA, USA]), which are isolated from fermentation of CCH. Collagenase AUX-I and AUX-II are two different single polypeptide chains consisting of approximately 1000 amino acids with a molecular weight of 114 and 113 kDa, respectively [49]. These two classes appear to differ primarily in substrate specificity [51]. AUX-I collagenases are highly specific with respect to their proteolytic targets, with high affinity for the intact, triple-helical collagen, acting primarily at the N-and C-terminal domains. AUX-II collagenases generally exhibit less substrate specificity, target internal peptide sequences for cleavage, and demonstrate higher affinity for small peptides and denatured collagen. Together, AUX-I and II synergistically hydrolyze the triple helical conformation of collagen, enzymatically destroying collagen deposits (FIGURE 1) [51,52]. Affected substrates include collagen-I, III and IV, fibronectin and desmin, among others [53]. The proposed beneficial effects of CCH in PD are based on its observed effect on collagen types I and III, which are the predominant collagen identified in PD plaques [26]. As collagen types I, III and IV are also identified in numerous additional structures, including vessels and basement membranes, this may account for the AEs observed, including hematomas and ecchymoses.

AUX-I and AUX-II collagenases are not immunologically cross-reactive, and active catalytic and collagen-binding domains are required for their catalytic activity against collagen [101]. Additionally, calcium and zinc are needed as metal cofactors to facilitate the enzymatic process [101]. Since CCH selectively lyses collagen at the site of injection (i.e., PD plaque) [54], systemic administration is not required for therapeutic efficacy [101].

Systemic dissemination of CCH is minimal, with a study of 20 DC patients undergoing single intralesional injections of CCH (0.58 mg) yielding no quantifiable levels of enzyme AUX-I or AUX-II in the serum at 30 days postinjection [49]. In a pharmacokinetic study of 20 patients with PD, patients received two injections of CCH 0.58 mg 24 h apart, followed by plaque modeling 24 h after the second injection [102]. Similar to the DC study, the concentration of the two enzymes were found to be low, detected only following the 0.5-h postinjection, and were not quantifiable in the plasma after plaque modelling [102]. Furthermore, preclinical animal experiments demonstrated that there was no evidence of either immediate or delayed hypersensitivity reactions, despite repeated injections of CCH in the same animal over long periods of time [55]. Purified CCH was not mutagenic in *Salmonella typhimurium* (AMES test) and was not clastogenic in both an *in vivo* mouse micronucleus assay and an *in vitro* chromosomal aberration assay in human lymphocytes [49]. Additionally, CCH did not impair fertility in rats when administered intravenously at dosages equivalent to 45-times that of the human dose [49].

Clinical efficacy

Preclinical studies

CCH was first proposed in the 1980s as a potential collagenolytic agent with a possible role in

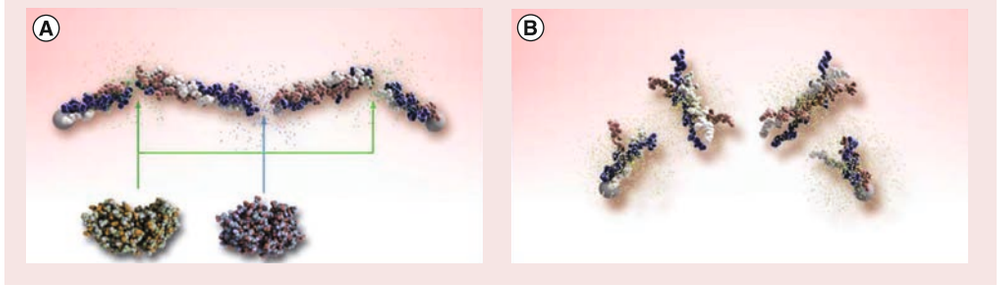

Figure 1. Representation of collagenase clostridium histolyticum's effects on collagen's triple helix structure. (A) Demonstrates Aux I and Aux II cleavage sites of the collagen triple helix. **(B)** Demonstrates postcleavage collagen remnants.
Reproduced with permission from [52].

the treatment of PD [56]. *In vitro* effectiveness of purified CCH was studied using samples of PD plaques from three patients, along with corpora cavernosal tissue and pericardium from a normal autopsy [54]. The study demonstrated that intralesional injection of CCH into the PD plaque specifically targets the collagen within the plaques and leads to a reduction of plaque size and widespread fraying and dispersal of collagen bundles. Histological studies on these specimens showed no degradation of elastic tissue and no structural damage to the nerve fibers and arteries/arterioles; however, some dissolution of the perineurium and small venules was noted. Another study of the effects of collagenase in a rat tail demonstrated that the enzymatic effects of collagenase were confined to 0.5 cm proximal and distal to the site of injection, supporting the conclusion that CCHs catalytic effects are focal and confined to the injection site [57]. It has been demonstrated that the majority of the collagenolytic activity of CCH occurs in the first 24 h following administration, with dry weights obtained of PD plaques demonstrating an 88.6% reduction, compared with 17% in tunica albuginea controls [54]. *In vitro* modeling of the efficacy of CCH demonstrates a dose-dependent effect on Dupuytren's cords and fascial nodules obtained from DC patients, a finding that is likely translatable to the PD population given the histologic similarities [48,57].

Phase I clinical studies

The first Phase I clinical trial in men with PD was an open-label study in 31 men with a mean age of 55.5 years and a history of PD ranging from 2 to 60 months [58]. The mean follow-up was 9.8 months (range: 4–15 months). A total of 30 out of 31 patients (97%) reported a history of painful erections followed by the classic PD symptoms of penile deviation or circumferential constriction. Pain precluded intercourse in four out of 31 patients (13%) and three out of 31 patients (10%) reported buckling of the penis upon intromission. Ten of the 31 patients had received prior treatment, including vitamin E, intralesional corticosteroids, irradiation, ultrasound and potassium aminobenzoate without subjective improvement. Collagenase was injected intralesionally at a concentration of 470–620 µ/cc in the first 15 patients. The dose was then escalated to 910 µ/cc in the next 16 patients. Objective improvement was observed in 20 of 31 patients (65%), predominantly observed within 2 weeks of treatment, with complete disappearance or significant alteration of the plaque in four out of the 20 patients. In the remaining 16 patients, curvature deformity was decreased by 20–100%. Erectile pain was eliminated in 13 of 14 patients (93%). A subset analysis demonstrated that three of the four patients (75%) who were unable to achieve intromission regained this ability. Very few significant AEs were noted during the study, including injection site pain in two patients and ecchymosis in 21 patients. Injection site corporeal rupture was reported in one patient, during sexual intercourse two weeks after treatment. The patient was treated by bandaging the penis and avoidance of erections for 3 weeks. Interestingly, after healing, curvature deformity was noted to be straighter than before rupture.

Results from the previous study led to the second Phase I study, a prospective, randomized, double-blind, placebo-controlled study of 49 men with PD aged 28–66 years [59]. This study was designed to compare the hydraulic and pharmacologic effects among three different volumes and concentrations of CCH. The three different volumes and concentrations of CCH that were used included: first, three aliquots of 6000 units; second, five aliquots of 10,000 units; and third, seven aliquots of 14,000 units. Patients were stratified into three groups based on curvature deformity and disease severity (plaque size). CCH-treated patients showed improvements in curvature deformity and plaque size compared with placebo-treated patients. Greater improvements in curvature deformity were observed in patients with curvatures <30° compared with those with curvatures >60° (100 and 13%, respectively). No patient experienced progression or worsening of any disease parameter (e.g., pain, bending or ability for intercourse) within the 3-month follow-up.

To determine the immune response in patients receiving CCH injections for treatment of PD, serum samples were obtained from 44 patients before and at 1 and/or 2 months after intralesional injection of 3000–12,650 units of purified CCH [60]. Serum samples were also obtained from 150 untreated healthy control patients. IgG anticollagenase was detected in 34% of the 150 healthy controls and in 58% (24 out of 41) of patients with PD prior to treatment. Intralesional injection of CCH induced a two to tenfold increase in the IgG levels at 1–2 months in 88% of patients. Of the 186 individuals tested (142 controls and 44 with PD), one patient (0.5%) had detectable collagenase-specific IgE antibody. Findings suggested that the potential for development of severe immune responses was unlikely.

Phase II clinical studies

Two Phase II clinical trials were conducted on patients with PD (Table 1) [102,103]. In one Phase IIb, randomized, double-blind, placebo-controlled study, 147 patients with PD aged 45–64 years were stratified by the degree of curvature deformity into two groups: 30–60° or >60° [50]. Patients were randomized 3:1 in favor of CCH into four groups to receive intralesional CCH or placebo injections with or without penile plaque modeling (1:1) [50]. Treatments consisted of two intralesional injections of CCH into the primary plaque separated by 24–72 h. The treatment regimen was repeated after 6 weeks for a total of three cycles. Penile plaque modeling was performed 24–72 h after the second injection of CCH in each treatment cycle. Primary end points included safety (AEs), absolute and percentage change in penile curvature and change in total score for PD patient reported outcomes (PD-PRO). The mean ± standard deviation history of PD was 3.0 ± 2.7 versus 2.1 ± 1.3 years in patients in the CCH versus placebo (modeling) groups, respectively, and 3.0 ± 3.5 versus 2.2 ± 2.6 years in patients in the CCH versus placebo (without modeling) groups, respectively. Change in curvature deformity among patients in the CCH treatment group was observed beginning at week 6 and continued through week 36, with statistically significant changes over placebo seen at weeks 18, 24 and 36 ($p \leq 0.007$ at each time interval). At least a 25% improvement in curvature deformity was observed in 61% of CCH-treated patients versus 25% of placebo-treated patients, in addition to small changes in the mean penile length and plaque size. Responses to questionnaires demonstrated improvements in PD-PRO scores, specifically on the PD-PRO symptom bother domain, in CCH-treated patients compared with placebo-treated patients ($p = 0.05$). There were no statistically significant differences in the other three domains of the PD-PRO and in the International Index of Erectile Function scores. The most frequently reported AEs among patients in the CCH versus placebo groups were bruising (86.5 vs 44.4%; $p < 0.001$), edema (45.0 vs 0%; $p < 0.001$), pain (52.3 vs 11.1%; $p < 0.001$), contusion (14.4 vs 2.8%; $p = 0.07$) and penile

Table 1. Phase II studies evaluating the safety and effectiveness of collagenase clostridium histolyticum for the treatment of Peyronie's disease.

Study designation	AUX-CC-801 [50]	AUX-CC-805 [102]
Design	Randomized, double-blind, placebo-controlled	Open-label (pharmacokinetics)
Number of patients (received CCH injections)†	n = 147 (111)	n = 20 (20)
Age range (years)	45–64	38–75
Key eligibility criteria	Diagnosis of PD for ≥6 months, in a stable relationship for ≥3 months before screening, penile curvature of ≥30° and ≤90°	Symptom(s) 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°
Treatment cycles‡	Three treatment cycles, 6 weeks apart, two injections/cycle	One cycle, two injections/cycle§
Study objectives	To assess the treatment sensitivity of the PD-PRO questionnaire; to assess the effectiveness of CCH in improving penile curvature in men with PD; and to assess the safety of CCH in men with PD	To determine if there was systemic exposure following a single treatment cycle in men with PD; and to evaluate the safety of CCH in these patients
Geographic locations (number of sites)	USA and Australia (multisite; 12 in the USA)	USA (1)
Study duration	9 months	29 days

†Each injection contained 0.58 mg (10,000 units) of CCH.
‡In all Phase IIb studies, penile plaque modeling was conducted 24–72 h after the last injection in each treatment cycle. In study AUX-CC-801, patients were randomized 1:1 to plaque modeling vs non-modeling, and each group was further randomized 3:1 to CCH vs placebo.
§Patients received two injections in one treatment cycle for pharmacokinetics analyses and were rolled into AUX-CC-805 and received up to three additional treatment cycles.
CCH: Collagenase clostridium histolyticum; PD: Peyronie's disease; PD-PRO: Peyronie's disease patient reported outcomes.

edema/pain(9.9 vs 0%; p = 0.07 each). At week 36, all CCH-treated patients tested positive for AUX-I and AUX-II antibodies; however, there were no reports of systemic immunological AEs.

Phase III clinical studies

Two Phase III clinical trials were conducted to evaluate the safety and efficacy of CCH in patients with PD (Table 2) [37]. The Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies I and II (IMPRESS I and II) were randomized, multicenter, double-blind, placebo-controlled studies. IMPRESS I and II were conducted in parallel and involved 64 sites in the USA and Australia. In combination with objective measures of penile deformity, the PDQ was used within the IMPRESS studies as a measure of the psychological aspects of PD. The PDQ is a 15 question self-reported, disease-specific questionnaire, which measures the impact and severity of PD symptoms in three domains: first, psychological and physical symptoms; second, penile pain; and finally, symptom bother [36]. PDQ has been validated in the IMPRESS I and II studies [37]. Primary end points were safety (treatment-related AEs), percentage change in penile curvature and change from baseline in the PD symptom bother domain.

In the IMPRESS studies, men with a mean age of 57.6 ± 8.5 years and a mean duration of PD of 4.1 ± 4.1 years, were stratified by baseline curvature deformity (30–60° vs 61–90°), and were randomized to CCH or placebo (2:1 in favor of CCH) [37]. Treatment cycles were the same as in the Phase IIb study; however, patients could receive up to four treatment cycles. Penile

Table 2. Phase III studies evaluating the safety and effectiveness of collagenase clostridium histolyticum in the treatment of Peyronie's disease.

Study designation	AUX-CC-803† [37]	AUX-CC-804† [37]
Design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
Number of patients (received CCH injections)‡	n = 417 (277)	n = 415 (274)
Age, range in years	CCH: 28–79 Placebo: 30–81	CCH: 23–84 Placebo: 33–78
Key eligibility criteria	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°	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°
Treatment cycles§	Four cycles, 6 weeks apart, two injections/cycle	Four cycles, 6 weeks apart, two injections/cycle
Study objectives	Primary: to evaluate effectiveness of CCH in the treatment of PD Secondary: to evaluate (1) reduction in the severity of PD physical and psychological symptoms; (2) change in the penile pain domain of the PDQ; (3) responder analysis based on subject global assessment; (4) change in the overall satisfaction domain of the IIEF; (5) change in penile plaque consistency; (6) change in penile length; (7) safety of CCH in men with PD	Primary: to evaluate effectiveness of CCH in the treatment of PD Secondary: to evaluate (1) reduction in the severity of PD physical and psychological symptoms; (2) change in the penile pain domain of the PDQ; (3) responder analysis based on subject global assessment; (4) change in the overall satisfaction domain of the IIEF; (5) change in penile plaque consistency; (6) change in penile length; (7) safety of CCH in men with PD
Geographic locations (number of sites)	USA and Australia (32)	USA and Australia (32)
Study duration (months)	12	12

†Two identical studies.
‡Each injection contained 0.58 mg (10,000 units) of CCH.
§Penile plaque modeling was conducted 24–72 h after the last injection in each treatment cycle.
CCH: Collagenase clostridium histolyticum; IIEF: International index of erectile function; PD: Peyronie's disease; PDQ: Peyronie's disease questionnaire.

plaque modeling was conducted approximately 24–72 h after the second injection of each cycle by the investigator or qualified clinician. Patients were instructed to continue with an in-home penile plaque modeling procedure three-times daily for the 6-week period between treatment cycles. Additional treatment cycles were not administered if penile curvature deformity was reduced to <15° or if the investigator determined further treatment was not clinically indicated. The combined analyses of IMPRESS I and II demonstrated a mean percent improvement of 34% in penile curvature deformity (mean degree change per subject of -17.0 ± 14.8°) in the CCH-treated patients versus 18.2% improvement (mean degree change per subject of -9.3 ± 13.6°) in placebo-treated patients ($p < 0.0001$). As a coprimary end point in the IMPRESS studies, the PD symptom bother domain score was measured. The mean change in PD symptom bother domain score demonstrated a statistically significant improvement in the CCH-treated patients of 2.8 ± 3.8 versus placebo-treated patients 1.8 ± 3.5 ($p = 0.0037$). Treatment-related AEs remained localized to the penis and groin, and were mild or moderate in severity. Approximately 79% of the AEs resolved without intervention within 14 days. Serious AEs (SAEs) consisted of corporal rupture in three patients and penile hematoma in three patients. Three corporal ruptures and one hematoma were surgically repaired, one hematoma resolved spontaneously and one was treated with aspiration. At week 52, 99.2 and 98.4% of patients tested positive for AUX-I and AUX-II antibodies, respectively, with no reports of systemic immunological AEs. In addition to the objective changes in penile curvature, results from these two trials demonstrated the clinical utility of the PDQ as a valuable diagnostic tool and outcome measure for assessing treatment-related improvements in PD symptoms [36].

Safety & tolerability

Data addressing the safety of CCH in four Phase II (n = 166) and three Phase III (n = 788) clinical trials, both published and unpublished, were combined in an integrated safety analysis study [61]. A total of 6701 injections of collagenase were used to treat 954 patients with PD; 65.4% of patients received four treatment cycles (eight injections), 87.2% of patients completed their assigned study and 12.8% of patients were prematurely discontinued. Overall, 93.7% of CCH-treated patients reported at least one nonserious AE. All common AEs (>5% incidence) were either local to the penis or at the injection site. A total of 58 (6.1%) CCH-treated patients experienced at least one nonfatal SAE, of whom eight (13.7%) patients experienced drug-related SAEs (four penile hematomas and four corporal ruptures). Treatment was interrupted in seven out of these eight patients. There were no events of systemic hypersensitivity reported in the integrated safety analysis population.

Conclusion

The introduction of CCH offers a novel, office-based approach for DC. Pending FDA approval, CCH is expected to have a similar role in the treatment of patients with PD. CCH is a highly concentrated combination of active isoforms of AUX-I and AUX-II, and functions by cleaving collagen fibers [49]. The specificity of CCH is secondary to its increased activity against collagen types I and III and decreased activity against type IV, which is predominantly present in the basement membrane of neurovascular structures [52]. This likely accounts for the observed minimal collateral damage to the perineurium and small venules with preservation of surrounding elastic tissues, nerve fibers and arteries/arterioles [54].

CCH has undergone extensive evaluation, with multiple, well-designed Phase I–III trials reporting outcomes. In adults with PD, CCH is effective in improving penile curvature (mean 34% [17.0 ± 14.8°] vs placebo 18.2% [9.3 ± 13.6°]) and PDQ patient-reported PD symptom bother domain scores (2.8 ± 3.8 vs placebo 1.8 ± 3.5) [37,50]. Preliminary studies evaluating the use of CCH in PD patients have demonstrated good safety and tolerability profiles [37,50,61]. Long-term safety, efficacy and comparison studies are warranted.

Future perspective

PD is a relatively common disorder affecting a sizable proportion of the population, and is associated with a significant reduction in quality of life. The investigational CCH therapy is currently undergoing FDA review for the treatment of PD, with a decision anticipated before the end of 2013. As CCH represents the most highly studied nonsurgical therapy for PD, pending approval, its integration into routine clinical practice is anticipated. With increasing clinical experience, optimal treatment strategies will continue to evolve, with further studies performed to assess the efficacy with varied patient disease characteristics (acuity of disease, complex curvatures and calcifications)

and administration schedules/doses. Comparison studies with existing nonsurgical therapies, including existing intralesional agents, will help to provide the appropriate clinical context for the use of CCH in current treatment algorithms.

Disclosure

This manuscript was prepared according to the International Society for Medical Publication Professionals' Good Publication Practice for Communicating Company-Sponsored Medical Research: the GPP2 Guidelines.

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Executive summary

Mechanism of action

- Collagenase clostridium histolyticum (CCH) is a fixed-dose mixture of clostridial collagenase type I (AUX-I) and type II (AUX-II) isoforms that act synergistically to locally degrade collagen.
- AUX-I collagenase degrades the triple-helical structure of intact collagen, primarily at the N- and C-terminal domains.
- AUX-II collagenase degrades denatured collagen and internal peptide sequences.
- Type IV collagen (component perineurium and vessel adventitia) is relatively spared by this combination of collagenase isoforms.

Pharmacokinetic properties

- The degradative effects of CCH are confined to the region of injection.
- Injected CCH is inactivated at the site of injection within 24 h of administration.
- CCH is rapidly (0.5-h postinjection) cleared from the plasma.
- Penile plaque modeling does not result in release of measurable amounts of CCH.

Clinical efficacy

- Consistent straightening of penile curvature deformity associated with Peyronie's disease (PD) has been demonstrated in Phase II and Phase III clinical trials (CCH mean 34% [17.0 ± 14.8°] vs placebo 18.2% [9.3 ± 13.6°]).
- Reproducible improvements in the patient-reported PD symptom bother score of the PD Questionnaire have also been shown in the Phase III clinical trials (CCH mean 2.8 ± 3.8 vs placebo 1.8 ± 3.5).
- CCH provides an alternative, nonsurgical treatment option for patients with PD.
- Long-term efficacy and recurrence rates are yet to be established.

Safety & tolerability

- Most treatment-related adverse events (AEs) are mild-to-moderate in severity, and localized to the site of injection in the penis or groin.
- The most common treatment-related AEs, occurring in ≥25% of patients, include penile hematoma, penile pain, penile swelling and injection site pain.
- Serious treatment-related AEs are rare and include penile hematoma and corporal rupture.
- Most subjects developed positive antibodies to AUX-I and AUX-II; however, there was no impact on the safety profile.
- None of the reported treatment-emergent AEs were indicative of a severe systemic immunological response.

Drug interactions

- The tetracycline family of antibiotics have been shown to inhibit matrix metalloproteinase-mediated collagen degradation *in vitro* and may present a potential, although unproven, interaction.

Dosage & administration

- CCH is administered as a 0.58 mg dose injected directly into the penile plaque.
- Treatment cycle consists of two injections, approximately 24–72 h apart.
- Treatment cycles can be repeated for up to four cycles, each separated by approximately 6 weeks.
- Manual penile plaque modeling should be performed by a clinician 24–72 h after the second injection of each treatment cycle and every day at home by the patient.

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