Peyronie's Disease and Injectable Collagenase *Clostridium histolyticum*: Safety, Efficacy, and Improvements in Subjective Symptoms

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OBJECTIVE To report on an early adopter series of collagenase *Clostridium histolyticum* (CCh) for Peyronie's disease (PD). Postapproval studies of CCh have been anticipated after recent Food and Drug Administration authorization of its use for men with PD as definitive and durable nonsurgical interventions have been long desired.

MATERIALS AND METHODS From May 2014 to October 2015, a database consisting of PD patients with >30° of penile curvature received CCh from a single provider at a single institution. Objective penile curvature measurements and deformity directions were assessed pre- and posttreatment. Using the validated Peyronie's Disease Questionnaire (PDQ), changes in subjective symptoms of intercourse ability, penile pain, and bother were also noted.

RESULTS We followed 49 unique PD patients treated with CCh. Mean follow-up was 183 days with a median of 6 injections over 3 cycles performed per patient. The mean pretreatment penile curvature was 49.3 degrees. Curvature was reduced by 15.4 degrees (32.4%, $P < .01$) after therapy. There were 10 out of 22 patients who regained ability to perform vaginal intercourse. Subjectively, there was an improvement in the ability to perform intercourse (29.1% improvement, $P < .01$) and bother symptoms (mean decrease 43.2%, $P < .01$), but no significant changes in penile pain ($P = .89$). Five notable bleeding events (10.2%) were noted, including 1 penile fracture requiring operative exploration.

CONCLUSION CCh use for PD yielded improvements in penile curvature, subjective intercourse, and bother symptoms. Further postanalysis studies of greater follow-up are needed to assess long-term durability, efficacy, and safety. UROLOGY 94: 143–147, 2016. © 2016 Elsevier Inc.

The hallmark of Peyronie's disease (PD) is an inelastic fibrous scar linked to a history of penile trauma with abnormal wound healing and pathogenic response of the fibrotic cascade.[1,2] The prevalence of symptomatic disease has varied from 0.5% to 13% in recent series and has been thought to be underestimated.[3] In diseased histologic specimens, tunical collagen demonstrates irregular distributions of types I, III, and V subtypes instead of the typical fibrillary type I array intercalated with elastin fibers.[4] Transforming growth factor beta 1 upregulation leads to pathologic extracellular remodeling with inappropriate fibrin deposition, decreased elastin content, fibroblast infiltration, and inhibition of endogenous collagenase.[5-7]

Attempting to halt this vicious cycle of extracellular remodeling, exogenous bacterial collagenase *Clostridium histolyticum* (CCh) has been studied and approved by the Food and Drug Administration (FDA) in December of 2013 for treating PD. This approval stemmed from successful phase 2b and phase 3 trials from Gelbard et al, which showed significant improvements in penile curvature (mean 16.3 and 17.0 degrees reduction respectively) with a 1.5% incidence of serious adverse events such as corporal ruptures or clinically significant penile hematomas in the treatment arm.[8,9] In addition, the industry trials introduced a validated Peyronie's Disease Questionnaire (PDQ) that quantified improvements in bother scores after treatment.[10]

After FDA approval, CCh (trademarked as Xiaflex) has been offered to authorized providers across the country. There is since a paucity of postapproval trials to validate the industry findings. Ziegelmann et al provided 1 of the first series with 69 patients undergoing CCh injections with a 23° mean objective curvature reduction and significant improvement in mean patient perceived improvement after 2 injection trials. Seven patients developed penile

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hematomas (10%) without any reports of fracture or tunical rupture.[11]

The aim of our study was to provide independent validation of CCh use for PD patients for a single- institution, single-provider series. We sought to assess objective improvements in penile curvature, subjective changes according to the PDQ, and safety profile after the injections.

MATERIALS AND METHODS

From May 2014 to October 2015, men undergoing CCh injections for PD were prospectively followed in a single-provider, single-institution series at a tertiary care medical center. Inclusion criteria followed label indications per Auxilium Pharmaceuticals, Inc. of a palpable plaque and a curvature of at least 30 degrees.[12] Trimix (30 mg/mL papaverine, 1 mg/mL phentolamine, 10 mcg/mL alprostadil) was administered in a multidosing strategy in an effort to attain a "best quality erection." Five units of Trimix was injected at 10-minute intervals to a maximum of 15 units. Goniometry measurement was performed from coronal sulcus to the point of maximal curvature. Baseline PD characteristics were noted including the chronicity of presentation, with the active phase defined as the onset of symptoms within 1 year of the first CCh injection or subjective reports of deformity changes before the first injection. Previous therapies or any known progression to surgical management during the follow-up period were noted.

The PDQ was administered to patients on the day of the first injection of each cycle.[13] This validated questionnaire assessed changes across domains of intercourse and penetrative ability (6 questions, scored 0-4), pain (3 questions, scored 0-10), and bother/psychological symptoms (6 questions).

CCh injection methodology has been reported by the sole provider in this series.[14] Each cycle consisted of 2 CCh injections a day apart. Penile curvature measurements were performed on the day of the first injection of each cycle. Complete detumescence was achieved prior to any CCh application, sometimes with intracavernosal phenylephrine. CCh mixture (0.25 cc/0.58 mg) was injected with a 0.5-inch, 27-gauge needle transversely through the width of a palpable plaque but not completely passing through. Pressure was then firmly applied for 1 to 3 minutes to achieve hemostasis. A compressive dressing was used over the injection site for 2 hours. Penile modeling was carried out by the patient at home starting when penile bruising or puncture pain subsides, usually 1-3 days after the second injection of each cycle. Patients were instructed to stretch the penis longitudinally for 30 seconds, 3 times a day for 6-8 weeks until the subsequent injection cycle. Patients were also instructed to abstain from sexual activity for 2 weeks after each injection cycle.

Adverse events were recorded on follow-up patient encounters. Notable bleeding sequelae were defined as penile bruising (discoloration without palpable collection), penile hematoma (palpable collection), or penile fracture (corporal rupture of tunica albuginea). We defined significant adverse events as any event requiring an unforeseen office, emergency room visit, admission, or requiring operative repair.

Comparison between penile curvature measurements was described with a Student 2-tailed paired *t* test. Mean symptom scores from each domains of the PDQ (intercourse ability, penile pain, and bother) were also compared before and after treatment with a Student 2-tailed *t* test. All *P* values of <.05 were considered statistically significant. These analyses were performed through GraphPad's Quickcalcs interface (GraphPad Software 2016; San Diego, CA).

RESULTS

Baseline patient characteristics are described in Table 1. Over the course of 17 months, we followed 49 males with PD who had initial penile curvatures of at least 30 degrees and received at least 1 cycle of CCh. A median of 6 injections across 3 cycles were performed. Specifically at the conclusion of this analysis, 3 patients completed 1 cycle, 22 patients completed 2 cycles, 10 patients completed 3 cycles, 13 patients completed the prescriber-recommended 4 cycles, and 1 patient received 5 cycles due to patient request. Six patients completed their treatment course early due to marked improvement in penile curvature to a post-treatment measurement of ≤30° after 1 to 2 cycles of injections (mean curvature reduction of 31.4°). Mean follow-up time was 183 days (range: 43 to 426 days). There was a mean curvature decrease of 15.4° (range: increase of 10° to decrease of 60°, $P < .0001$) from the pretreatment measurement to the most recent curvature assessment. This reflected a 32.4% mean decrease in penile curvature (interquartile range 5% to 25%). Ten (20.4%) patients did not have any discernible changes in curvature or saw their deviation increase slightly after treatment (Fig. 1). A subset analysis was performed of 14 patients who underwent 4 or more cycles of injectable CCh, which was the recommended course according to the IMPRESS trial protocol.[9] This showed a similar trend of a 17.7° curvature improvement from a pretreatment curvature of 45.7° to a post-treatment curvature of 28.0° (38.7% change, $P < .001$).

Regarding subjective data from the PDQ, 24 patients provided both pretreatment and posttreatment surveys (Fig. 2). If treatment was ongoing, data from the latest cycle were reported. After CCh therapy, there was a statistically significant improvement in the ability to perform intercourse across 4 questions (mean "problem" decrease of 29.1%, $P < .0001$) and bother symptoms across 4 questions (mean bother symptoms decrease of 43.2%, $P < .0001$). There was no difference in penile pain symptoms across 10 questions ($P = .89$). As the PDQ was only administered

Table 1. Baseline patient demographics and characteristics of their Peyronie's disease (n = 49)

Mean age (range)	59.3 years	37.2-81.7 years
Mean initial curvature (range)	49.3°	30-100°
Stable disease (%)	37	75.5
Prior oral therapy (%)	26	53.1
Prior intralesional verapamil therapy (%)	2	4.1
Isolated dorsal curvature (%)	35	71.4
Dorsal curvature with secondary curvature (%)	5	10.2
Isolated left curvature (%)	4	8.2
Isolated right curvature (%)	4	8.2
Isolated ventral curvature (%)	1	2.0
Presence of hourglass deformity (%)	11	22.4