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PEYRONIE'S DISEASE

Treatment of Peyronie's Disease With Collagenase *Clostridium histolyticum* and Vacuum Therapy: A Randomized, Open-Label Pilot Study

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ABSTRACT

Background: Collagenase *Clostridium histolyticum* (CCH) is indicated for the treatment of penile curvature in adult men with Peyronie's disease (PD) with palpable plaque and curvature deformity of at least 30° at the start of therapy.

Aim: To evaluate the efficacy and safety of CCH plus vacuum-pump therapy with and without penile modeling for the management of PD.

Methods: Adult men with PD and penile curvature of at least 30° were randomly assigned to receive CCH 0.58 mg plus vacuum therapy alone (n = 15) or with penile plaque modeling (n = 15). Patients received no more than four treatment cycles (cycle = ~6-week duration), each consisting of two intralesional injections of CCH administered 24 to 72 hours apart. Vacuum therapy was applied twice daily from 14 days after the second injection of each cycle until the following cycle. Modeling was performed 24 to 72 hours after the second injection of each cycle.

Outcomes: The primary end point was change in penile curvature from baseline to week 36; additional end points included changes in Peyronie's Disease Questionnaire (PDQ) domain scores, composite response (≥20% decrease in penile curvature and decrease in PDQ bother score ≥ 1 point), and global response (small but important, moderate, or much improvement in the Global Assessment of PD).

Results: At week 36, improvement in penile curvature from baseline was similar in the two groups (mean change from baseline = −23.7° [SD = 10.9] for CCH + vacuum + modeling and −23.3° [SD = 7.2] for CCH + vacuum; between-group difference = −0.3°, 95% CI = −7.3 to 6.6). Improvements in most PDQ domains, including bother, were observed from baseline to week 36 in the two groups. Most patients were composite (66.7% and 84.6% with CCH + vacuum + modeling and CCH + vacuum, respectively) and global (86.7% and 92.3%, respectively) responders. The most common adverse events were penile contusion, penile swelling, and penile pain.

Clinical Implications: Vacuum-pump therapy administered alone or in combination with modeling after CCH treatment could improve PD symptoms.

Strengths and Limitations: This was a pilot study with a small sample and limited follow-up duration.

Conclusion: CCH and vacuum-pump therapy (alone or combined with modeling) could be an appropriate consideration for men with PD and warrants further investigation. **Ralph DJ, Abdel Raheem A, Liu G. Treatment of Peyronie's Disease With Collagenase *Clostridium histolyticum* and Vacuum Therapy: A Randomized, Open-Label Pilot Study. J Sex Med 2017;14:1430−1437.**

Key Words: Collagenase; Modeling; Penile Fibromatosis; Male Urogenital Diseases; Hand-Operated Vacuum-Pump Therapy

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INTRODUCTION

Peyronie's disease (PD) is a fibrotic disorder of the penis that is believed to develop as a response to abnormal wound healing after trauma or microtrauma.[1] PD is characterized by fibrosis of the tunica albuginea, which results in the formation of plaque and the development of penile deformity (particularly curvature) that

might or might not be accompanied by pain.[1,2] Although once considered a rare condition, the current prevalence of PD could be as high as approximately 20%, depending on how the condition is defined and the population is studied.[2] The symptoms of PD, and the potential effect of the condition on erectile function, can cause marked psychosocial stress.[3] Importantly, in most cases, this stress persists throughout the course of the disease, indicating that men with PD do not naturally adapt to the psychological distress associated with the condition.[3] The management of stable PD consists of different pharmacologic and surgical approaches, depending on the severity of the penile deformity and associated symptoms.[1] Surgery is often reserved for the most serious cases[4]; however, evidence to support the efficacy of most current noninvasive or minimally invasive therapies is limited.[1,4]

Collagenase *Clostridium histolyticum* (CCH; Xiaflex, Endo Pharmaceuticals, Inc, Malvern, PA, USA) is a purified mixture of AUX-I and AUX-II collagenases from *C histolyticum* that hydrolyses collagen under physiologic conditions and results in lysis of collagen plaques.[5] CCH has been approved by the US Food and Drug Administration for the treatment of adult men with PD who have palpable collagenous plaques and penile curvature of at least 30° at the start of treatment. In a combined analysis of data from two large randomized, double-blinded, placebo-controlled trials, IMPRESS I and II, treatment with CCH resulted in a mean decrease in penile curvature of 34% compared with 18.2% in patients who received placebo ($P < .0001$).[4] In addition, CCH treatment was associated with significant improvements compared with placebo in the physical and psychological symptoms of PD.[4] Based on these findings, the American Urological Association has included CCH in its guidelines, to be used in combination with penile plaque remodeling, for the decrease of penile curvature in patients with stable PD, penile curvature of 30° to 90°, and intact erectile function.[2]

Another treatment strategy that has been shown to be potentially efficacious in decreasing penile curvature in patients with PD is vacuum-pump therapy.[6] Hence, the present pilot study was performed to investigate the effect of vacuum-pump therapy, with and without penile modeling, on the efficacy and safety of CCH administration for the management of PD.

METHODS

Study Design

The study was a prospective, randomized, open-label, pilot study conducted at a single site in the United Kingdom from October 2014 through March 2016 (ClinicalTrials.gov identifier NCT02267460). The study was conducted according to Good Clinical Practice guidelines and the principles of the Declaration of Helsinki, and the protocol was approved by the appropriate independent ethics committee.

Patients

Men (age $\geq$ 18 years) with stable symptomatic PD, as determined by the investigator, were eligible for inclusion if they had penile curvature of at least 30° in the dorsal, lateral, or dorsolateral plane and if it was possible to delineate the plane of maximal curvature. Principal exclusion criteria included penile curvature less than 30° or greater than 90° at screening; other penile disorders such as hourglass deformity, compromised penile hemodynamics, or significant erectile dysfunction that had failed to respond to oral phosphodiesterase type 5 inhibitors; history of spontaneous priapism; calcified plaque that would preclude correct administration of CCH; receipt of previous oral or intralesional medical therapies for PD within 3 months of the first dose of study drug or the use of mechanical devices within 2 weeks of screening; and previous surgery for PD. Written informed consent was obtained from all patients before inclusion in the study.

Treatments

Once patients met the entry criteria, an investigator requested randomization of the patients into treatment groups through an interactive web response system. Patients were stratified according to the degree of baseline penile curvature (30−60° or >60°) and randomly assigned (1:1), through an interactive web response system using a computer-generated randomization allocation sequence with a block size of 4, to receive CCH plus vacuum-pump therapy with investigator-administered plaque modeling or CCH plus vacuum-pump therapy alone. Because of the nature of the interventions, no blinding took place. Each treatment cycle consisted of two intralesional injections of CCH 0.58 mg separated by approximately 24 to 72 hours. Injections were given directly into the primary penile plaque. Up to four approximately 6-week treatment cycles (ie, eight injections) could be given, with intervals of 42 $\pm$ 5 days between cycles, if penile curvature of at least 15° remained and the investigator considered that further treatment was clinically indicated.

Vacuum-pump therapy was performed using the ErecAid Esteem manual vacuum therapy system (Timm Medical Technologies, Inc, Fort Washington, PA, USA). Patients were instructed to use the pump twice daily (morning and evening) from 14 $\pm$ 2 days after the second injection of CCH in each treatment cycle until the start of the next cycle. Vacuum-pump therapy was continued until the first follow-up visit (nominal week 24). Before the first use of the system, all patients received training in the correct operation of the system and were required to demonstrate that they could use the system safely and correctly. For each application of vacuum therapy, a vacuum was created for 5 to 10 seconds until an adequate erection was obtained. Tension rings or other devices were not used to aid erection. Once the penis was erect, the vacuum was maintained for 30 seconds before release. These steps were performed five times during each treatment session.

Plaque modeling by the investigator or other designated personnel was performed 24 to 72 hours after the second injection of CCH in each treatment cycle. Local anesthesia before modeling was given if requested by the patient. During modeling, the investigator grasped the hardened portion or