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SYSTEMATIC REVIEWS

Use of intralesional collagenase in the treatment of peyronie's disease: A review

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Abstract

AIM: To review the relevant literature in an effort to examine the body of evidence available to date.

METHODS: Ovid MEDLINE search database was queried using MeSH terms "penile induration", "peyronie's disease", "Collagenases" and "Collagenase" using various permutations. No temporal parameters were employed.

RESULTS: In all, 5 relevant clinical trials were isolated from 34 results. These trials were analyzed using the Oxford Centre for Evidence-Based Medicine criteria. They were further examined based on study design and methods; the primary and secondary outcomes were reviewed for treatment efficacy and collagenase-related side effects.

CONCLUSION: Intralesional collagenase appears to be safe and effective in the non-surgical treatment of Peyronie's disease. However, the data remains limited and further inquiries into the safety of collagenase, treatment standardization and standardized outcomes reporting remain necessary. Furthermore, studies comparing intralesional collagenase to alternative medical and surgical therapy will be important in guiding the future treatment decision process.

Key words: Peyronie's disease; Collagenase; Reconstructive urology; Plaque; Intralesional injection

Core tip: In December of 2013, the United States Food and Drug Administration approved the use of collagenase clostridium histolyticum (CCH) for the treatment of Peyronie's disease (PD). In all, 5 relevant clinical trials were isolated from 34 results. With limited data on medical PD treatments, the studies to date appear to support CCH as a reasonably safe and well-tolerated non-surgical intervention. However, because no studies compared CCH to other medical interventions and no trials have been conducted to assess the ultimate need for surgical intervention, further comparative investigations are necessary to determine the ultimate role that the intralesional collagenase may play in the treatment of PD.

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INTRODUCTION

In December of 2013, the United States Food and Drug Administration (FDA) approved the use of collagenase clostridium histolyticum (CCH) for the treatment of Peyronie's disease (PD). This approval was based on several clinical trials, most notably the recently completed

concurrently run Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies (IMPRESS) I and Ⅱ trials. The goal of this paper is to describe the body of evidence leading to the FDA's approval of this drug in the treatment of PD.

The prevalence of PD is strikingly high with epidemiological estimates ranging from 3.2% in Europe[1] to 8.9% in the United States[2]. Yet despite its high prevalence, PD remains both underreported and difficult to treat[3,4]. Many men do not seek treatment, oftentimes due to embarrassment or lack of access to accurate information. The presentation of PD is varied and includes penile pain with erection, angulation of the penis, erectile dysfunction, and the presence of a palpable plaque, typically located on the dorsum of the penis[5-10]. Furthermore, men with PD are at a higher likelihood to have an inability to perform intercourse as curvature of 60 degrees of higher has been associated with a threefold increase in the odds of sexual disability[11]. These factors and the complicated nature of PD make it psychologically and physically detrimental to not only the patient but also his sexual partner[12,13].

Although 250 years have passed since Francois Gigot de la Peyronie described the first case series of PD, little understanding of its etiology has emerged[14,15]. The disease is believed to occur secondary to abnormal collagen deposition and scar formation from buckling trauma to the tunica albuginea of the penis. The current pathophysiological model of PD reflects the body's response to microtrauma to the tunica albuginea where a disordered healing process allows scarring to occur. This scarring restricts symmetrical expansion of the tunica albuginea during an erection, thus resulting in angulation of the penis. As with all scar formation, the major step is collagen synthesis. It is theorized that microtrauma combined with an underlying genetic predisposition allows for abnormal collagen deposition and scar formation[16].

The formation of scar is a balance between collagen formation and its degradation through collagenase-a naturally occurring enzyme that functions to break down collagen. This enzyme, produced by humans, is also formed by bacteria. Clostridium histolyticum, a gram-positive anaerobic bacterium, is well known to cause destructive, rapidly spreading infections through soft tissue planes which occurs mainly through the function of collagenase. This bacterial enzyme was first isolated in 1953[17]. It has since been purified and is now commercially available. CCH (Xiaflex, Auxillium Pharmaceuticals) is a purified mixture of two collagenases, AUX-1 and AUX-2. The first *in vitro* biochemical study of CCH, published in 1962, demonstrated collagenolytic activity on animal tissues[18]. Gelbard *et al*[19] subsequently examined the *in vitro* effects of CCH on the tunica albuginea of patients with and without PD. Their research demonstrated a significant collagenolytic effect of CCH on both normal tissue and tissue with Peyronie's plaques. Importantly, vascular smooth muscle was not digested and preservation of all vessels except small venules was observed. This led to the notion that collagenase would be a safe treatment for PD and other similar afflictions, including Dupuytren's disease (DD).

In February 2010, CCH was approved by the FDA for treatment of DD. The approval came as a result of a large double blind randomized, placebo controlled trial (DBRCT)[20] demonstrating that localized injection of CCH, in conjunction with passive joint manipulation, reduced the contracture to full extension within 30 d of last injection, compared to placebo (from 43.9 to 80.7 degrees *vs* from 45.3 to 49.5 degrees, $P < 0.001$). This observation was achieved with minimal adverse events (AEs). The pathological and epidemiological similarity between DD and PD and the promising of DD trials lead to the initiation of two DBRCTs to examine the effects of CCH on PD[21].

MATERIALS AND METHODS

Relevant articles for this review were obtained through the Ovid MEDLINE search database. Search strategy included MeSH terms "penile induration", "peyronie's disease", "Collagenases" and "Collagenase". The search was carried out as follows: ("penile induration" OR "Peyronie's disease") AND ("Collagenases" OR "collagenase"). This produced in 34 results, which were further narrowed down by clinical trials focusing on collagenase and PD yielding a total of five relevant trials. Due to the limited availability of clinical trials on this subject, no year limits were used in this search and publication dates ranged from 1985 through 2013.

Evaluation of these clinical trials was based on the Oxford Centre for Evidence-Based Medicine criteria.

RESULTS

A total of 5 clinical trials have examined the use of CCH in the treatment of PD (Tables 1-4).

The use of collagenase in the treatment of PD

The first clinical trial examined the safety of intralesional collagenase to treat PD[22]. It included 31 men, each with a mean curvature of 42 degrees, 10 of which had undergone prior non-CCH treatments for their condition. Collagenase was injected daily for three days at a dose of 470 to 620 μg/mL for the first 15 patients and 910 μg/mL for the rest. Total dose ranged between 470 to 2730 μg/mL per patient, with a mean of 2330 μg/mL. This low dosing regimen was chosen to assess both safety and efficacy during this phase 1 trial. Objective improvement was observed in 20 patients; 4 had resolution of their plaques, and 16 had penile curvature reduction by 20%-100%. These results were seen in the majority of patients within 2 wk of treatment. Pain with erection was eliminated in 13 of the 14 patients who entered this study with erectile pain. Three out of 4 men who were unable to have intercourse regained the ability after treatment. The one who failed had a pre-treatment 180-degree penile bend. AEs

Table 1 Study designs

Ref.	No. of patients	Study design	Length of study	Control group	Length of follow up
Gelbard *et al*[22]	31	Prospective	Mean of 22 mo per patient	None	9.8 mo (mean)
Gelbard *et al*[23]	49	Double blind, RCT	3 mo	Placebo	3 mo
Jordan[24]	25	Prospective	9 mo	None	None
Gelbard *et al*[25]	147	Double blind, RCT	Up to 18 wk	Placebo	None
Gelbard *et al*[26]	832	Double blind, RCT	Up to 52 wk	Placebo	None

RCT: Randomised controlled clinical trial.

Table 2 Study treatments

Ref.	Intralesional injection therapy dose and schedule
Gelbard *et al*[22]	One daily dose of 470620 μg/mL (15 patients) or 910 μg/mL (16 patients) for three consecutive days
Gelbard *et al*[23]	CCH single injection (6000-14000 Units)
Jordan[24]	Three 10000 Units injections administered over 7-10 d, repeated at 3 mo
Gelbard *et al*[25]	CCH 0.58 mg (10000 Units), 2 injections 24-72 h apart, repeated every 6 wk for up to 3 cycles
Gelbard *et al*[26]	CCH 0.58 mg (10000 Units), 2 injections 24-72 h apart, repeated every 6 wk for up to 4 cycles

CCH: Collagenase clostridium histolyticum.

Table 3 Adverse events

Ref.	Adverse effects (*n*)
Gelbard *et al*[22]	Ecchymosis (21), Pain (2), Albuginea rupture (1)
Gelbard *et al*[23]	Tenderness at injection site (Majority), tunica albuginea rupture (1)
Jordan[24]	Edema/pain/or ecchymosis (20), No serious AEs
Gelbard *et al*[25]	Bruising (96), Edema (50), Pain (58), No serious AEs
Gelbard *et al*[26]	Ecchymosis (441), Edema (30), Pain (250), Corporeal rupture (3), Penile hematoma (3)

AEs: Adverse events.

Table 4 Study outcomes

Ref.	Outcome	Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence
Gelbard *et al*[22]	Improvement seen in 20 patients (4 had plaque disappearance, 16 had curvature decrease by 20%-100%)	2
Gelbard *et al*[23]	Overall, 36% responsed to treatment. Improvement greatest in patients with lesser degree of pre-treatment curvature	2
Jordan[24]	Significant mean changes from baseline angular deviation and plaque width at 3, 6, and 9 mo	2
Gelbard *et al*[25]	Improved penile curvature (29.7% *vs* 11.0%, $P < 0.05$) and patient reported bother scores for treatment group *vs* placebo	1
Gelbard *et al*[26]	Improved penile curvature (34% *vs* 18%, $P < 0.0001$) and patient reported symtom bother score for treatment group *vs* placebo	1

were minimal and included ecchymosis (21 patients) and pain (2 patients). One patient had an albuginea rupture two weeks after treatment. This was a 23 years old who experienced pain with a popping sensation during intercourse. The penis was bandaged and he was instructed to avoid intercourse for 3 wk. After healing, the degree of penile curvature was straighter than before treatment. Mean follow up for this study was 9.8 mo.

Collagenase vs placebo in the treatment of PD: A double-blind study

Eight years later, a trial of 49 patients was conducted stratifying patients by degree of curvature. The patients were divided into three groups: group 1; 30 degrees or less and/or palpable plaque less than 2 cm, group 2; 30 to 60 degrees and/or plaque 2 to 4 cm, group 3; over 60 degrees and/or plaque greater than 4 cm[23]. Pre and post intervention deformity was measured with vacuum induced erection photography. The patients in each group were randomized to receive either treatment or placebo (saline injections). The three treatment groups received a total of 6000 units, 10000 units, 14000 units, respectively. All injections were administered into the Peyronie's plaque, and patients were instructed to avoid intercourse for 2

wk after treatment. Patients were evaluated at 1 week, 1 mo, and 3 mo after treatment. Overall, 36 percent (8 of 22 patients) of the treatment group responded to CCH, compared to 4 percent (1 of 27 patients) for placebo, $P < 0.007$. In general, patients from group 1 had a higher response rate to CCH compared to group 2 and 3 (100%, 36%, 13%, respectively). Response differences for treatment *vs* placebo in groups 1 and 3 were not statistically significant. One category 3 patient experienced a tear of the tunica albuginea during intercourse 3 wk after treatment. The tear was treated conservatively and resolved. The majority of patients experienced tenderness at the injection site, yet this AE was observed as frequently in both the treatment and placebo groups.

The use of intralesional clostridial collagenase injection therapy for PD: A prospective, single-center, non-placebo-controlled study

A 2008 prospective trial including 25 patients with PD was conducted with a more uniform treatment protocol: three injections of intralesional CCH at 10000 units/0.25 cm^3 per dose, administered over 7-10 d[24]. This process was repeated at 3 mo after first treatment. Plaque size and angle deformity was assessed at 3, 6, and 9 mo. Eighteen of the 25 patients completed the treatment and follow-up. Primary outcome was a > 25% reduction from pretreatment angular deviation, considered a successful response. A secondary end point was a patient questionnaire. This questionnaire included a subjective patient evaluation of both visual outcomes and restoration of sexual function. Results demonstrated significant decreases in mean deviation angle observed at months 3 and 6 (*P*-values at 9 mo were not reported). Positive treatment response for the primary outcome (> 25% angular reduction) peaked at month 3 yet declined by month 9, likely due to drop-out of successful patients. However, patients who experienced treatment success in month 3 continued to experience success at month 9. Additionally, significant decreases were observed in plaque width at 3, 6, and 9 mo and plaque length at months 3 and 6. The patient questionnaire revealed overall global evaluations of the patient's disease condition improved. More than 50% were considered "much improved" or "very much improved". One third responded "minimal improvement" or "no change". AEs occurred in eighty percent of patients and included edema, penile pain, or ecchymosis. No serious AEs were observed.

As stated previously, by February, CCH had been FDA approved to treat DD at a dose of 10000 Units per injection. Studies have shown that intralesional injection followed by finger extension and manipulation, intended to further break down the cord, had shown the greatest improvement in plaque breakdown[20]. These protocols were thus applied to studies regarding CCH and PD.

Phase 2b study of the clinical efficacy and safety of CCH in patients with Peyronie's disease

A phase 2b DBRCT study including 147 subjects examined the effect of CCH and "modeling," or bending of the flaccid penis in order to break up a PD plaque[25]. Subjects were divided into 4 groups to receive CCH or placebo (saline injections) (3:1 randomization) with or without penile plaque modeling (1:1 randomization). Penile plaque modeling consisted of stretching the penis for 30 s, followed by 30 s in the nonmodeled state, repeated for 3 cycles at a time. Subjects in the CCH group received 2 injections at 10000 units/0.25 cm^3 per dose, given 24 to 72 h apart, repeated for up to 3 cycles at 6-wk intervals. Outcomes included change in penile curvature based on goniometer measurement, patient reported outcomes *via* questionnaire (PD-PRO and IIEF), and AEs. There were significant differences in penile curvature in the CCH *vs* placebo groups when modeling was applied (32.5% *vs* 2.5%, $P < 0.001$). Minimal difference was observed between treatment and placebo groups in the absence of modeling. Patient questionnaires revealed that CCH treated patients has a significantly better PD symptom bother score than those on placebo ($P = 0.05$). However there was no significant difference in the other questionnaire domains (intercourse discomfort, constraint, penile pain). Common AEs in CCH groups included bruising (86.5%), edema (45%), and pain (52.3%). No serious AEs related to treatment were observed. No systemic immunologic events were reported.

Clinical efficacy, safety and tolerability of CCH for the treatment of peyronie's disease in 2 large double-blind, randomized, placebo controlled phase 3 studies

Most recently, the Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies (IMPRESS) I and Ⅱ trial, a phase 3 DBRCT with the largest cohort of 832 subjects, examined CCH *vs* placebo in patients with PD[26]. Modeling was not performed. Dosing and scheduling was identical to the prior phase 2b study, although cycles could be repeated up to 4 times. Subjects treated with CCH had a mean 34% improvement in curvature, compared with 18% in the placebo group ($P < 0.0001$). PD symptom bother score was also significantly improved in the treatment *vs* placebo groups ($P = 0.0037$). AEs in the CCH group were similar to those observed in the phase 2b trial, including ecchymosis (80%), edema (55%), and pain (45.4%). However, six serious AEs were observed. Three men experienced corporeal rupture, all of which were successfully repaired surgically. The other three experienced penile hematoma, one resolving without intervention, one resolved with aspiration, and one successfully repaired surgically. No systemic or immunologic events were observed.

DISCUSSION

The recent FDA approval of CCH for the treatment of PD marks an important step in the treatment of this widespread and often debilitating disease. CCH is the first non-surgical therapy to become FDA approved for this purpose. Though limited clinical data currently ex-

ists on intralesional collagenase-in all, 5 clinical trials were isolated-the results appear promising. Though side effects throughout the trials were relatively common, they were mild and transient. Serious AEs were rare, and included corporeal rupture and penile hematoma. These serious AEs were reported both in the trials from 1985, 1993, and the most recent IMPRESS trial.

Improvement in penile curvature, both objective and subjective, was reported in all five trials; the highest level of objectivity was reached in the IMPRESS trial through the use of goniometer. Most importantly, two thirds of the sexually active men in the IMPRESS trial cohort received a validated PD symptom questionnaire taking into account the psychological burden that PD has on the patient.

There are limitations to this area of research. Although results support CCH as safe and effective, none of these trials compared CCH to other treatment modalities, or to placebo. Furthermore, the same team of researchers authored 4 out of 5 publications, which could contribute to bias. Yet given the excellent safety results, coupled with its efficacy displayed in DD trials, the authors of this paper still recommend CCH as a safe and effective treatment option for PD.

To date, no studies comparing CCH to other medical interventions have been conducted and no assessment of the ultimate need for surgical intervention has been performed. However, given the paucity of data on medical PD treatments, the studies to date appear to support CCH as a reasonably safe and well-tolerated non-surgical intervention for PD.

COMMENTS

Background

Trials on the use of intralesional collagenase for the non-surgical treatment of Peyronie's disease (PD) first appeared in 1985. However, in the three decades leading up to the United States Food and Drug Administration's (FDA) approval of this therapy, limited studies have been conducted to measure its efficacy and safety. Furthermore, few, if any review articles are available regarding this therapy.

Research frontiers

Collagenase clostridium histolyticum (CCH) was recently FDA approved for the treatment of PD. There have been a handful of trials focusing on the use of CCH to treat PD, yet few examined the safety and efficacy of CCH. To the authors' knowledge, there have been few, if any, review articles discussing these trials in detail, including CCH background, safety, efficacy, and future directions of research.

Innovations and breakthroughs

CCH is a promising, non-surgical alternative to treat PD. This review article discusses the CCH background, summarizes clinical trial results, and comments on future research directions. The authors believe this is a novel article and one that can help provide useful information to both clinicians and researchers who aim to treat this disease.

Applications

This article provides summaries of the efficacy, safety, and future directions of intralesional collagenase. This information can be applied to clinical practice, as well as future research.

Terminology

There are no terms in this article which the authors feel cannot be understood by the majority of readers.

Peer review

This article summarize the five clinical trials published from 1985 to 2013 about safety and advantage in the use of CCH in the treatment of PD. The studies support CCH as a reasonably safe and well-tolerated non-surgical intervention for PD: rare serious adverse events included corporeal rupture and penile hematoma.

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