World Journal of Urology
https://doi.org/10.1007/s00345-019-02850-3

TOPIC PAPER

Characteristics predictive of response to collagenase clostridium histolyticum for Peyronie's disease: a review of the literature

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Received: 1 March 2019 / Accepted: 11 June 2019

Abstract

Purpose To evaluate characteristics predictive of successful treatment outcomes of Peyronie's disease (PD) with collagenase clostridium histolyticum (CCH)

Methods CCH is the only FDA-approved medication for treating PD. We reviewed the literature that addresses pre-treatment clinical characteristics that may predict favorable response to CCH therapy.

Results Despite significant heterogeneity in reporting treatment success, we identified four well-studied characteristics that may be predictive of favorable response to CCH therapy: baseline penile curvature, baseline IIEF, duration of PD, and presence of calcification. CCH demonstrated a favorable response in those with pre-treatment curvature 30°–60°, longer duration of disease, mild to moderate baseline sexual function, and low calcification within plaques. Of all factors, calcification is emerging as the most significant factor likely because CCH is unable to degrade the calcified plaques. There is difficulty interpreting results because of differences in reporting outcomes. Some studies compared treatment groups to placebo, others reported changes in curvature, while others reported > 20% curvature correction as treatment success. Additionally, not all studies reported outcomes after completion of four cycles of CCH, and recent studies utilized a shortened, high dose, modified protocol.

Conclusions The ideal candidate for CCH therapy remains elusive. Based on the available literature, the man with PD who will have the greatest chance of curvature improvement will have curvature between 30° and 60°, longer duration of disease, an IIEF > 17, no calcification, and set to receive all four cycles. For a greater understanding of CCH treatment success in PD, prospectively collected registry reporting standardized outcomes are needed.

Keywords Peyronie's disease · Collagenase clostridium histolyticum · Xiaflex

Introduction

Peyronie's disease (PD) is an inflammatory condition of the corpus cavernosum leading to penile angulation, painful erections and impaired sexual function [1]. PD is characterized by an inelastic fibrous plaque in the tunica albuginea, the connective tissue that surrounds the corpus cavernosa [2]. Treatments are either surgical or medical. Surgical treatments for PD are tunical plication, plaque excision and grafting, or placement of a penile prosthesis (for those with erectile dysfunction) [1]. However, surgery carries a risk of penile shortening, altered penile sensation and new onset erectile dysfunction. Only collagenase clostridium histolyticum (CCH) is food and drug administration (FDA) approved for the treatment of PD and is recommended by both the AUA and EAU guidelines in appropriacy selected patients [1]. AUA guidelines also recommend other medical treatments such as oral NSAIDs to treat pain symptoms, and off label intralesional injections of interferon α-2b and verapamil [1].

Collagenase clostridium histolyticum (CCH) was FDA approved for the treatment of PD in December 2013 after the publication of two large randomized placebo-controlled studies titled Investigation for maximal Peyronie's reduction efficacy and safety studies (IMPRESS) [3]. Currently, CCH remains the only FDA-approved medication for the treatment of PD. CCH treatment is time and labor intensive consisting of multiple injections spaced out over 24 weeks. Unfortunately, meaningful improvements in penile curvature

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Published online: 26 June 2019

and sexual function are not guaranteed. IMPRESS trial analysis showed a significant mean curvature improvement of − 17.0° and 34%, and a 2.8-point improvement in the Peyronie's disease questionnaire (PDQ) [3].

After the publication of IMPRESS, additional studies confirmed the safety and efficacy of CCH [4]. The IMPRESS trials reported improvements in degrees of curvature, PDQ scores and percentage curvature change from baseline to assess treatment success [3]. More recently, authors reported the number or percentage of patients who improve by > 20% from baseline as a successful outcome [4–6]. This heterogeneity in outcome reporting creates difficulty in data interpretation and study comparison. However, studies consistently report that not all men who receive CCH improve. Additionally, improvements considered significant do not always result in a return to penetrative sexual activity. Therefore, identifying pre-treatment characteristics predictive of favorable response to CCH is imperative. In this literature review, we will evaluate pre-treatment patient characteristics that multiple studies found predictive of favorable response to CCH therapy for PD.

Methods

We performed a PubMed and Google scholar search for articles addressing the use of CCH in PD that reported outcomes based on pre-treatment characteristics. We used the search terms collagenase clostridium histolyticum, Xiaflex and Peyronie or Peyronie's Disease. We included studies published in English that involved adult human subjects through November of 2018. We excluded any manuscripts that specifically treated men off label or were a review of the literature. We included studies that performed subgroup analysis to provide insight into which patients had greater improvements.

Baseline curvature

Penile curvature is the hallmark of PD and baseline curvature is reported in all studies for PD. Several studies assessed baseline penile curvature as a potential predictor of therapy response. Final curvature is an important determinant in the success of treatment, as curvature influences other symptoms of PD such as impaired sexual function, sense of embarrassment, and decreased quality of life. We expect that patients with a greater degree of curvature will exhibit greater degree curvature improvement; however, they may not have robust improvements in sexual function due to residual curvature. CCH is only approved for men with curvature between 30° and 90°; therefore, most studies that evaluated baseline curvature as a predictor of improvement grouped patients into 30°–60° and 60°–90°. In 1993, Gelbard et al. examined 49 men with curvature between 0° and 90° receiving CCH for PD. Subgroup analysis found that men with curvature between 0° and 60° had larger improvements compared to men with curvature > 60° [7]. However, this study was small, including men with curvature between 0° and 30° and adjusted CCH doses based on curvature and palpable plaque size (larger plaques and greater curvature received higher doses), thus making these results difficult to apply to current treatment guidelines. In 2015, post hoc analysis of the IMPRESS trials showed significant curvature improvements regardless of baseline curvature compared to placebo. Larger percentage curvature improvements occurred with less severe curvature (− 14.8° and 33.8% for 30°–60° baseline curvature) but men with worse curvature achieved larger degree improvements (− 25.5° and 23.3% for 61°–90° baseline curvature) [8]. When evaluating PD bother scores, a significant improvement occurred in the 30°–60° group compared to placebo; however, no improvement in PD bother was observed in the 61°–90° curvature group. These data suggest that despite statistically significant improvement in penile curvature for the 60°–90° group, bother remains. Unfortunately, these studies did not assess return to penetrative sexual activity or change in IIEF as a function of baseline curvature. Wymer et al. studied 115 men and used > 20% curvature reduction as their primary success outcome. In their study, 75% of men with curvature > 60° improved compared to only 48% in the 30°–60° group ($p = 0.01$)[5]. However, this seemingly greater improvement in the > 60° baseline curvature is likely the result of the criteria chosen to asses curvature reduction. Improvement by 20% for someone with 90° curvature (18° difference, or 72° final curvature) may not be as meaningful for someone who improves by 20% with 40° curvature (8° difference, or 32° final curvature). A 20% curvature improvement does not assure improvement in PD bother, sexual function or return to penetrative intercourse. In summary, studies show curvature improvements, regardless of baseline curvature (Table 1). However, it appears that larger percentage curvature and PD bother score improvements were seen in men with 30°–60°. What remains unstudied is assessment of return to sexual function and IIEF as a function of baseline curvature.

Duration of disease

Duration of disease emerged as another possible predictor of response to CCH. PD is categorized into active and stable phase. Active phase disease is characterized by inflammation, pain and developing curvature. Stable phase generally occurs by 12 months when patients no longer see a change in deformity. Early studies of CCH excluded men with active

Table 1 Summary of studies included with relevant outcomes

Author	Year	Study *N*	Study type	Groups	Improvement measured	Other outcomes	Comparison group	Limitation
Baseline curvature								
Gelbard	1993	49	Prospective randomized placebo controlled double-blinded	0–60° > 60°	More favorable improvement		Placebo	Treatments were adjusted for plaque size and curvature, not reflective of current practice
Lipshultz	2015	621	Post hoc analysis	30°–60° 61°–90°	− 14.8° and 33.8% reduction − 25.5° and 23.3% reduction	Improved bother score	Placebo and within	Retrospective
Wymer	2018	115	Single arm rospective cohort	30°–60° > 60°	75% improved by > 20% 48% improved by > 20%		Within groups	No placebo control
Duration of disease								
Goldstein	2013	776	Prospective cohort	1–2 years > 4 years	28.6% reduction 38.9% reduction		No control group	No statistics presented
Lipshultz	2015	621	Post hoc analysis	1 to < 2 years < 4 years > 4 years	No improvement − 36.6° − 14.0°	3 point improvement in bother 1.6 point improvement in bother	Placebo and within	Retrospective
Levine	2015	147	Single arm prospective cohort	6 to < 12 months > 12 months	− 19.4° and 38% reduction − 15.2° and 27.6% reduction		Placebo	Did not compare treatments groups
Cocci	2018	135	Single arm prospective cohort	< 12 months ≥ 12 months	54.9% improved by > 20% 58.3% improved by > 20%		Within groups	No placebo control, did not meet statistical power
Wymer	2018	115	Single arm prospective cohort	< 2 years > 2 years	No difference		Within groups	
Baseline sexual function								
Lipshultz	2015	621	Post hoc analysis	IIEF ≥ 17 IIEF 6–16 IIEF 1–5	− 35.6% No change in curvature No change in curvature		Placebo and within	Retrospective
Cocci	2017	135	Single arm prospective cohort	Mean IIEF 23	IIEF increased by 5.32	− 19.07° curvature	None	Used a "Modified protocol", no placebo
Diao	2017	51	Retrospective Cohort	IIEF 17.2	No change in IIEF	− 19.2° curvature	None	Retorspective, no placebo
Anaissie	2017	76	Single arm prospective cohort	> 45° < 45°	− 0.18 in IIEF + 3.00 In IIEF		Within groups	No placebo control
Raheem	2017	53	Single arm prospective cohort	EF 20.9 IS 7.7 OS 5.0	EF increased to 23.8 IS increased to 9.4 OS increased to 6.8	− 17.2° curvature	Within groups	Used a "Modified protocol", no placebo, utilized vacuum assist devices

Table 1 (continued)

Author	Year	Study *N*	Study type	Groups	Improvement measured	Other outcomes	Comparison group	Limitation
Capece	2018	135	Single arm prospective cohort	EF 23.4 IS 9.9 OS 8.6	EF increased to 25.0 IS increased to 11.4 OS increased to 9.8	− 19.52° curvature	Within groups	Used a "Modified protocol", no placebo, utilized vacuum assist devices
Plaque calcification								
Goldstein	2013	776	Prospective randomized placebo controlled double-blinded	No calcification Continuous calcification	34.8% reduction 27.0% reduction		Within groups	No statistics presented
Lipshultz	2015	621	Post hoc analysis	No calcification Calcified	− 17.2° and 34.3% reduction No improvement	2.9 point improvement in bother	Placebo and within	Retrospective
Wymer	2018	115	Single arm prospective cohort	No calcification Calcified No calcification Severe calcification	67% improved by > 20% 41% improved by > 20% 28.1% reduction 10.3% reduction		Within groups	No placebo control

phase PD because up to 12% have spontaneous resolution of deformity without any intervention [9]. Current FDA recommendations do not include CCH for active phase disease and, therefore, most studies exclude men with symptoms for less than 12 months. Disease duration may affect outcomes because of differences in plaque consistency. Plaques of different age may have different susceptibility to the lytic effects of CCH based on changes in plaque composition over time.

In a 2013 abstract, Goldstein et al. evaluated disease duration and response to CCH in 776 men. They concluded that all men improve regardless of disease duration, demonstrating greater improvement in men with > 4 years duration compared to < 4 years. However in their presentation, they did not present statistical significance or compare treatment to a placebo group [10]. In 2015, post hoc analysis of the IMPRESS trials found greater percentage improvements in penile curvature (− 39.6° vs − 14.0°) and PD bother scores (− 3.0 vs − 1.6) with longer duration (> 4 years) of disease compared to those treated with placebo. Interestingly, no significant improvement was seen for men with symptoms 1 to ≤ 2 years [8]. This study reinforced the idea that men with longer disease duration have greater improvement. In 2015, Levine presented an abstract evaluating 147 men with PD assigned to CCH or placebo, of which 36 men had PD symptoms for 6 to < 12 months. In the men with PD for less than 12 months, the CCH group ($n = 22$) had significant improvement (− 19.4° and 38% vs − 8.9° and 19.8%) compared to placebo ($n = 12$). This result was reported as similar to the greater than 12 month duration group (− 15.2° and 27.6% for CCH vs − 3.9° and 7.3% for placebo) [11]. Although this abstract did not directly compare treatment groups to each other. In 2017, Cocci et al. published a study using Raheem's "modified protocol" in men with stable disease of duration < 12 months ($n = 51$) and ≥ 12 months ($n = 84$). In this study, both groups had significant improvement in curvature. No difference was found between the shorter or longer duration group: change from baseline penile curvature by ≥ 20° was achieved in 58.3% of men with duration ≥ 12, compared to patients 54.9% with < 12 months ($p = 0.7$) [6, 12]. Similarly, Wymer et al. treated 115 men with at least 2 cycles of CCH and did not find disease duration to be predictive of curvature improvement > 20% [5]. In summary, studies on duration of disease remain mixed. Men appear to respond to CCH regardless of duration, but men with longer duration seem to have larger improvements (Table 1). Future studies evaluating changes in plaques at a tissue level may provide insight into some of the observed results.

Baseline sexual function

Baseline sexual function is an important aspect of PD. The AUA guideline on PD recommends penile prosthesis surgery to patients with Peyronie's disease and erectile dysfunction (ED) and/or penile deformity sufficient to prevent coitus despite pharmacotherapy and/or vacuum device therapy [1]. Therefore, men with significant ED are generally excluded from trials evaluating CCH. The most widely utilized questionnaire for erectile dysfunction is the international index

of erectile function (IIEF). Some assessed baseline IIEF as a predictor of curvature improvement while others evaluated changes in IIEF after CCH therapy as an endpoint. Post hoc analysis of the IMPRESS trials found that men with higher IIEF scores (IIEF ≥ 17) had the greatest percentage improvements in penile curvature (− 35.6% vs − 17.9%) and PD bother score (− 2.7 and − 1.6) compared to placebo. Men with lower IIEF scores between 1–5 (no sexual function) and 6–16 (low erectile function) had no change in penile curvature or PD bother score compared to placebo. This result may be because those with higher IIEF scores obtain frequent erections which may assist in modeling, or that men with lower IIEF may have unassessed medical chromobodies that affect vascularity and wound healing.

Later, Cocci et al. evaluated IIEF-15 and curvature in 135 patients who received treatment consisting of three intralesional injections of CCH on the high-dose "modified protocol". After the treatment, IIEF-15 score has increased by a mean of 5.32, IIEF-EF (erectile function) improved by 1.6, and curvature decreased by − 19.07° (15.0–20.0) [6]. This study demonstrated significant changes in both IIEF scores and penile curvature from baseline. It is important to note that the median baseline IIEF-EF score of participants was 23, classifying them as no baseline erectile dysfunction. In contrast to Cocci, Diao et al. evaluated a cohort of 51 patients and found no significant change in IIEF score after therapy (17.2 ± 5.7 to 17.8 ± 4.9) [13]. Despite no change in IIEF, there was a significant change in curvature (60° ± 16.9° to 40.8° ± 14.9°, $p < 0.0001$). These inconsistent improvements in IIEF scores may be due to concurrent treatment for mild erectile dysfunction. We cannot assume that curvature is the only factor affecting erectile and sexual function in patients with PD. If patients have underlying organic or vasogenic ED, correction of curvature may not improve IIEF.

Using a different approach to assessing CCH results, in 2017 Anaissie et al. published a study of 76 men focusing on the impact of the number of cycles of CCH injections. They hypothesized that more injections of CCH lead to greater improvements in curvature. They concluded that regardless of the number of cycles, patients with a baseline curvature of > 45° demonstrated a greater improvement in IIEF score than those patients with a baseline curvature of < 45°. Although these results were not statistically significant (− 0.18 vs + 3.00, respectively, $p = 0.073$), the authors noted that their results were nearing significance and likely would improve with greater sample size [14]. The study reported an overall curvature improvement from 58.2° (pre-treatment) to 41.0° (post-treatment).

Because sexual function emerged as an important independent outcome of CCH success, Raheem et al. evaluated changes in specific IIEF domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction after three injections of CCH on the "modified protocol". The mean baseline IIEF scores were 20.92 classifying the patients as mild erectile dysfunction. Significant improvements were observed in erectile function (20.9–23.8, $p < 0.001$), intercourse satisfaction (7.7–9.4, $p < 0.01$, and the overall satisfaction (5.0–6.8, $p < 0.001$). These men also achieved a reduction in penile curvature from 54.2° (30°–90°) to 37.0° (12°–57°). In a prospective, non-randomized multicentric study, Capece et al. showed similar results to the Raheem study. Mean pre-treatment curvature improved from 48.89° to 29.37° with significant improvements in all IIEF questionnaire domains after three injections: erectile function (23.4–25.0), orgasmic function (8.9–9.7), sexual desire (8.6–9.7), intercourse satisfaction (9.9–11.4) and overall satisfaction (8.6–9.8) [15]. It is important to note that the baseline IIEF score in this study was 23.4, which is classified as no erectile dysfunction. Although improvements were statistically significant, they may not have clinical significance. This study is among the only to evaluate patients with good baseline erectile function. CCH does not appear to worsen men who already achieve good erections.

In summary, subjects with mild to almost no erectile dysfunction show the most improvement with CCH therapy and CCH did not worsen erectile function (Table 1). Improvements in IIEF may be due to restoration of penetrative sex with improvement in curvature, decreased pain with intercourse, and improved self-image. Many of these studies reported significant improvements in penile curvature which may likely explain the significant improvements in IIEF scores.

Plaque calcification

Plaque calcification was recognized early on as a poor predictor of CCH therapy response. Initially, severe calcification too dense for needle passage was an exclusion criterion for the IMPRESS trials. If the needle cannot penetrate, effective delivery of CCH is not assured. Despite this, calcification is not considered an exclusion criterion for CCH in the treatment of PD. When evaluating the literature on calcification, difficulty in translatability exists as there are no accepted definitions for degree or severity of calcification. Additionally, AUA guidelines do not mandate the use of penile ultrasound to identify, document, or classify calcification [1]. In Goldstein's 2013 abstract, calcification was defined as no calcification, noncontiguous stippling, and contiguous calcification [10]. Curvature Improvements were observed in all groups regardless of calcification level, with greater percentage improvement seen with less calcification (34.8% in non-calcified vs. 27.0% in contiguous calcification). Unfortunately, statistical analysis was not presented to

assess if these group differences were significant. However, this study does provide some evidence that greater calcification could be a poor prognostic factor for treatment outcomes. Post hoc analysis of the IMPRESS trials used a similar calcification criterion as Goldstein. In this study, only men without calcification ($n=287$) experienced significant improvements in curvature deformity (− 17.2° and 34.3% for CCH vs − 8.9° and 16.8% for placebo) and PD symptom bother (− 2.9 CCH vs − 1.7 placebo) when compared to placebo ($n=160$) [8], thus providing further evidence supporting success in treatment with less calcification. Wymer et al. prospectively collected data on 115 patients receiving CCH for PD. In this study, calcification was defined as: none, mild (stippled calcification of any size without shadowing), moderate (identifiable shadowing < 1 cm in size), or severe (identifiable shadowing > 1 cm in size). Of the 115 men, 34 (29.6%) had calcified plaques. Improvement was defined as a > 20% curvature decrease. More patients with non-calcified plaques had successful treatment than those with calcified plaques (67% vs 41%, $p=0.01$). In subset analysis, they found that compared to the men without calcification, those with severe calcification ($n=7$) had significantly less overall percent curvature improvement (28.1% vs. 10.3%, $p=0.04$.) and less return to penetrative intercourse [5]. In summary, calcification appears to be the strongest predictor of poor response to CCH (Table 1).

Other factors

Other lesser studied factors may or may impact CCH success. Cocci et al. suggested that plaque location may affect response to CCH, with basal plaques being most favorable [6]. Wymer assessed patient age and direction of curvature (dorsal vs lateral) without finding significant differences in curvature correction [16]. Hertzman in an AUA abstract also showed no differences in curvature improvement when assessing patient age or history of diabetes mellitus [17].

Conclusions

The ideal candidate for CCH therapy remains elusive. The majority of studies evaluated are retrospective and were not powered to detect significance in subgroup analysis. Additionally, the definition of successful treatment varies with almost no studies evaluating return to sexual function as an outcome. Based on the available literature, the man with the greatest chance of curvature improvement has curvature between 30° and 60°, longer duration of disease, an IIEF > 17, and no calcification, and receives all four cycles (Table 2). Nonetheless, curvature and PDQ improvements occurred in men with vastly different characteristics. For a greater understanding, prospectively collected registry studies are needed.

Table 2 Proposed "ideal patient" for treatment of Peyronie's disease with collagenase clostridium histolyticum (CCH)

Ideal candidate for CCH	
Characteristic	
Baseline curvature	30–60°
Duration of disease	> 12 months
Baseline sexual function	IIEF > 17
Plaque calcification	None

Author contributions TM: Project development, data collection, data analysis, and manuscript writing/editing. AR: Project development, data collection, data analysis, and manuscript writing/editing. RR: Project development, data collection, data analysis, and manuscript writing/editing.

Funding No funding was provided for this project.

Compliance with ethical standards

Conflict of interest Authors TM and RR are recipients of an investigator-initiated research grant from Endo Pharmaceuticals. University of Miami is the recipient of a fellowship grant from Endo Pharmaceuticals.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent This study is a review of the literature and did not directly involve patients. No additional informed consent was obtained.

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