REVIEW

Collagenase *Clostridium histolyticum* in the treatment of Peyronie's disease: patient selection and perspectives

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Abstract: The safety and efficacy of the use of collagenase *Clostridium histolyticum* (CCH) for the treatment of Peyronie's disease has been confirmed over the past several years. However, identification of the ideal patient population for use of this treatment is not well established. Multiple studies have attempted to delineate various patient-specific factors that may predict response to treatment with CCH, with the intent of enhancing patient selection. To date, these include baseline curvature severity, duration of disease, disease phase at presentation, plaque calcification, baseline erectile function, plaque size, age, comorbid diabetes, previous penile trauma, responsiveness to first treatment cycle, baseline penile shortening or pain, prior treatment with intralesional injection, compliance with plaque modeling, and atypical curvature. In addition, other studies have sought to explore various aspects of treatment with CCH that may affect patient perspective of treatment. They have focused on patient-reported outcomes, female partner considerations, cost of treatment, and potential confounders of patient satisfaction. This review provides a summary and analysis of currently available literature on topics of patient selection and perspectives in regard to treatment of Peyronie's disease with CCH.

Keywords: Peyronie's disease, collagenase *Clostridium histolyticum*, Peyronie's disease questionnaire, curvature deformity, intralesional injection, erectile function

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Introduction

Peyronie's disease (PD) is a localized connective tissue disorder of the penis, characterized by aberrant formation of fibrous collagen-containing plaques within the tunica albuginea, leading to penile pain and deformity, sexual disability, and psychological bother.[1–11] Surgical intervention has historically been the standard of care but can be associated with significant morbidity.[12] Intralesional injection (ILI) is the sole nonsurgical therapy recommended to reduce penile deformity caused by PD. Currently, the only ILI approved by the US Food and Drug Administration (FDA) for the treatment of PD is collagenase *Clostridium histolyticum* (CCH) (Xiaflex; Endo Pharmaceuticals, Malvern, PA, USA), which carries a Grade B recommendation from the American Urological Association for the reduction of penile curvature and plaque size in PD patients.[13] This review provides an overview and analysis of the currently available literature on the topics of patient selection for and patient perspectives on the use of CCH for PD. CCH is a mixture of microbial collagenases that work synergistically to enzymatically degrade collagen fibrils composing PD plaques.[14] Its FDA approval followed publication of results from two landmark clinical trials assessing the use of CCH in PD patients.

Notable clinical trials and efficacy

Results from these two identical, prospective, multi-institutional, randomized, double-blinded placebo-controlled Phase III studies, entitled IMPRESS I and II (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies), were published in 2013. These studies enrolled a total of 832 males with PD, who were stratified by baseline penile curvature (30°–60° vs 61°–90°), and then randomized to CCH or placebo in a 2:1 ratio in favor of the former. Inclusion and exclusion criteria can be viewed in Table 1; these will be discussed separately. Participants underwent a maximum of four cycles of treatment at 6-week intervals, where each cycle consisted of two injections of 0.58 mg CCH or placebo separated by 24–72 hours, followed by penile plaque modeling 24–72 hours after the second injection. Subjects were instructed to perform standardized home penile modeling three times daily between each treatment cycle. Co-primary outcomes were percent change in penile curvature abnormality and the change in the Peyronie's Disease Questionnaire (PDQ) symptom bother score from baseline to 52 weeks. The PDQ, a highly sensitive, responsive, and reliable patient-reported outcome measure of PD, is a validated 15-question survey that measures the impact and severity of PD symptoms in three domains: 1) psychological and physical symptoms, 2) penile pain, and 3) symptom bother (Figures S1–S3).[15]

The PDQ symptom bother score reflects patient responses to queries regarding erection pain and appearance and the impact of PD on intercourse and its frequency. Seven secondary efficacy objectives were simultaneously investigated and are listed in Table 2. Post hoc meta-analysis of the two trials' combined data revealed that CCH-treated males had a mean 34% improvement in penile curvature (−17.0°±14.8° change), compared with a mean 18.2% improvement (−9.3°±13.6° change) in placebo-treated males ($P<0.0001$). The mean change in the PDQ symptom bother score was significantly improved in CCH-treated males vs placebo group (−2.8±3.8 vs −1.8±3.5; $P=0.0037$). In addition, with the exception of penile length and penile pain, all secondary endpoints were significantly improved in CCH-treated males compared to males in the placebo group.[16]

A more recent Phase III open-label study with n=347 published results in 2015 that provided evidence of reproducibility of the findings reported in the IMPRESS trials.[17] This study followed the same protocol as the IMPRESS trials, except it included patients who had been enrolled in a previous CCH pharmacokinetic study or had received placebo in an earlier Phase II CCH study, and it measured final outcomes at 36 weeks instead of 52 weeks. Data analysis revealed statistically significant mean improvements from baseline to week 36 in both percent change in penile curvature deformity

Table 1 Inclusion and exclusion criteria for the selection of study population in IMPRESS trials[25]

Inclusion criteria
- Healthy males aged 18+ years in a relationship with a female partner for at least 3 months and willing to have vaginal intercourse with that partner
- Diagnosis of PD for ≥12 months with evidence of disease stability
- Penile curvature ≥30° in a single plane, dorsal, lateral, or dorsolateral
- Signed consents for treatment and disclosure of PHI
- English-literate (rating instruments were written in English)

Exclusion criteria
- Penile curvature <30° or >90°
- Conditions affecting the penis, including but not limited to chordee, thrombosis of the dorsal penile artery, infiltration by a benign or malignant mass or an infectious agent, ventral curvature, isolated hourglass deformity, an active STD or immunodeficiency (including hepatitis B/C and HIV)
- Plaque located proximal to the base of the penis
- Calcified plaque (noncontiguous stippling was allowed)
- Failure to achieve erection sufficient to accurately measure the penile deformity (after administration of prostaglandin E or Trimix)
- ED unresponsive to PDE5 inhibitors
- Clinically significant compromised penile hemodynamics
- Treatment for PD, including but not limited to any previous surgery, previous use of CCH for PD, ESWT within 6 months, oral/topical agents within 3 months, ILI medical therapy within 3 months, an investigational drug/treatment within 1 month, or use of a mechanical device to induce passive erection within 2 weeks before the start of the study
- Allergy to CCH or other medications included in the protocol
- Uncontrolled hypertension, recent history of stroke, bleeding, or other significant medical condition making the subject unsuitable for enrollment
- Received anticoagulant medication during the 7 days prior to each dose of study drug (exception: ≤165 mg ASA daily, or ≤800 mg OTC NSAIDs daily)

Abbreviations: PD, Peyronie's Disease; PHI, protected health information; STD, sexually transmitted disease; HIV, human immunodeficiency virus; ED, erectile dysfunction; PDE5, phosphodiesterase type 5; CCH, collagenase *Clostridium histolyticum*; ESWT, extracorporeal shock wave therapy; ILI, intralesional injection; ASA, aspirin; OTC, over-the-counter; NSAID, nonsteroidal anti-inflammatory drug; IMPRESS, Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies.

Table 2 Secondary efficacy objective in the IMPRESS trials[25]

- Proportion of treatment responders
  - Assessed using the global assessment of PD (GAPD), a patient-reported rating scale assessing overall change in symptoms and effects of PD on the patient's life; ranges from −3 (much worse) to 3 (much improved)
  - Defined as a subject with a global score of at least 1 (improved in a small but important way)
- Decrease in severity of PD psychological and physical symptoms
- Assessed by the PDQ (evaluates the severity of physical symptoms and concerns of males with PD during vaginal intercourse)
- Change in the International Index of Erectile Function (IIEF) overall satisfaction domain
- Percent of composite responders as compared to placebo
  - Defined as ≥20% improvement in penile curvature and an improvement in the PDQ symptom bother score of ≥1 or a change from reporting no sexual activity at screening to reporting sexual activity
- Change in penile plaque consistency
- Change in penile length
- Change in the penile pain domain of the PDQ in subjects with a pain score of ≥4 at baseline screening

Abbreviations: PD, Peyronie's disease; GAPD, global assessment of PD; PDQ, PD Questionaire; IIEF, International Index of Erectile Function; IMPRESS, Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies.

(34.4%; corresponded to −18.3°±14.02° change in absolute curvature) and change in PD symptom bother score (−3.3), values that closely resembled those from the IMPRESS trials. Varying slightly from the IMPRESS trials, all seven secondary outcomes reached statistical significance in change from baseline, including penile length and pain.[17]

Notable clinical trials and safety

A pooled safety analysis of six clinical trials, including the above three, plus another randomized controlled trial and two more open-label studies, studied safety and tolerability outcomes for CCH in a total of 1,044 patients. At least one treatment-related adverse event (TRAE) was reported by 86% of males receiving CCH therapy, but the vast majority of TRAEs were deemed mild or moderate in severity (87%) and resolved spontaneously (79%). In the placebo-controlled studies, placebo-treated males also reported TRAEs, but to a significantly lesser extent than CCH-treated males. The most frequently reported TRAEs, each in ≥25% of CCH-treated patients, were penile ecchymosis, pain, and edema. Although 13% of the reported TRAEs were deemed severe, only nine patients had TRAEs that qualified as serious adverse events (SAEs), defined as an adverse event (AE) resulting in death, a life-threatening situation, inpatient hospitalization, or persistent or significant disability or incapacity. Penile hematoma formation accounted for five of these SAEs, and the remaining four were corporeal ruptures; all eventually

resolved, with only four of the nine SAEs requiring surgical intervention. The AE profile was similar following every injection, irrespective of the total number of injections given, indicating that AEs do not worsen or proliferate with increasing number of injections. Overall, <2% of the total analysis population prematurely discontinued treatment due to TRAEs. As another safety parameter, antibodies to and serum concentration of AUX-I and AUX-II were measured in study participants. Although >95% of the patients developed anti-AUX-I and anti-AUX-II antibodies by the end of their respective studies, there were no systemic immunological events reported, and no association between AEs and antibody levels was identified. AUX-I and AUX-II serum concentrations were uniformly low and transient.[14,16,17] Important to note in discussion of CCH safety, the retrospective analysis of males who received intralesional CCH and then proceeded to undergo surgical intervention for persistent penile curvature revealed that 100% of this cohort, albeit small (n=7), achieved reduction in curvature to <20°, required no increase in intraoperative time, and developed no extra AEs. These findings support the premise that surgical intervention following CCH treatment is safe and efficacious.[18]

IMPRESS trials inclusion and exclusion criteria

Although CCH's safety and efficacy for the treatment of PD were proven by the above studies, extrapolation of these findings to the general PD patient population is limited by the studies' stringent inclusion and exclusion criteria (Table 1).

Several of the criteria were selected because of the necessity of obtaining standardized objective measurements of penile curvature for data analysis. Inability to achieve a rigid erection would preclude measurement of the penile deformity, so those with compromised penile hemodynamics and refractory erectile dysfunction (ED) were excluded. Hourglass deformity characteristically lacks any measureable curvature. Plaque location proximal to the base of the penis would interfere with accurate curvature measurement. Uniplanar curvature was required because multiplanar curvature would have >1 point of maximal curvature and would yield >1 measurement of penile curvature. The presence of chordee would confound direction of curvature caused by the PD plaque.

Another criteria subset was chosen with the intention of minimizing potential confounding of treatment outcomes. Recent or concurrent treatment of PD with any other modality besides study-confined CCH would confound results.

Infiltration of the penis by a mass or infection may affect treatment efficacy. Likewise, disease stability was a requirement because it is thought that those in the active phase of the disease are more likely to experience spontaneous disease resolution or progression, which would confound the outcome measurements. Selection of the 12-month disease duration criterion was based on previous epidemiological studies that indicated that active disease typically lasts 12–18 months; consequently, a cutoff of at least 12 months' disease duration would ideally filter out many PD patients with active disease.

Other criteria were developed with concern to safety. Males had to be aged ≥18 years because no previous studies of CCH use in PD included children, so its safety in this population was not established. The same is true of patients with hourglass deformity and ventral curvature. Ventral plaques carried the additional theoretical possibility of urethral involvement, which was considered a contraindication to intralesional CCH therapy due to risk of urethral damage or stricture. Prior use of CCH for PD treatment, which could also play a confounding role, was grounds for exclusion because it is yet unknown whether excessive ILI with CCH is safe. Because CCH contains foreign proteins, severe allergic reactions can occur, particularly in patients with previous exposure to CCH for the treatment of Dupuytren's contracture. Anticoagulation therapy was included as an exclusion criterion due to bleeding risk. General health considerations precluded the inclusion of patients with significant comorbidities, as well as sexually transmitted diseases, for the joint safety of patients and providers; these comorbidities may also have contributed a confounding influence on treatment outcomes.

Two of the criteria addressed technical considerations of plaque injection. The tip of the needle had to be placed intralesionally, and medication injected directly in the center of the plaque; hence, anything preventing optimal ILI would be justification for ineligibility in the trial. Plaque calcification and plaque location proximal to the base of the penis were exclusion criteria for this reason. Injection of anesthetic would also interfere with injection into a plaque located proximal to the base of the penis.

One of the most prohibitive exclusion criteria, penile curvature <30°, was selected for a practical purpose. In the PD literature, 30° is the least severe curvature that has been proposed as a cutoff value for causality of sexual disability.[6,19] The trials using this criterion were attempting to market CCH therapy for PD as a clinically meaningful initiative to obtain FDA approval and subsequent insurance coverage. Accordingly, they chose to include only those PD patients who were physically disabled by their condition and stood to benefit in a medically quantifiable way (measureable improvement in sexual ability), as opposed to patients with milder curvature who were disturbed only by aesthetic appearance. The exclusion of penile curvature >90° was in effort to make the study population relatively homogenous by omitting the most severe cases of PD.

Finally, any of the aforementioned patient conditions that would inhibit their ability to have sexual intercourse would be doubly excluded, as one of the primary outcomes, PDQ symptom bother score, depended on the male's ability to have sex. This also explains why study participants had to be in a stable relationship and willing to have vaginal intercourse.[16,20,21]

Patient selection

Identification of patient-specific factors that can predict better or worse response to treatment can both inform patient selection for CCH use in the real-world practice setting and also help guide choice of inclusion and exclusion criteria for future CCH clinical trials. Several studies have examined various patient characteristics present at baseline or early in the CCH treatment process to determine whether they are independent positive or negative predictors of treatment outcomes, posttreatment satisfaction, and/or treatment tolerability. A few other studies have researched some of the populations excluded from the IMPRESS trials to assess efficacy and safety of CCH therapy in these specific populations, with the hope of broadening patient selection for use of CCH in PD.

Baseline curvature severity

Lipshultz et al[22] performed a subgroup analysis using IMPRESS trial data to stratify patients according to several separate parameters, one of them being baseline curvature severity. Patients were separated into two groups: 30°–60° and 61°–90°. Significant reduction in penile curvature was achieved in both subgroups in CCH-treated patients compared to placebo. Significant reduction in PDQ symptom bother score was achieved only in the subgroup with baseline 30°–60° curvature in CCH-treated patients compared to placebo. However, the improvement in PDQ symptom bother score in CCH-treated patients compared to placebo in 61°–90° subgroup was trending toward significance. Based on these results, CCH therapy may have a clinically useful role for PD patients with baseline severity of penile curvature ranging from 30° to 90°, but it is possible that patients with

more severe curvature at baseline may not derive a significant improvement in symptom bother from CCH treatment.[22]

Years before the IMPRESS trials, Gelbard et al[23] reported results from a single-center, prospective, randomized, placebo-controlled double-blinded Phase I study comparing efficacy and safety of CCH to placebo for the treatment of PD. The study population included PD patients with a mild degree of curvature at baseline (<30°). Patients were divided into three groups for analysis: 1) penile bend <30° and palpable plaque <2 cm, 2) penile bend 30°–60° and 2–4 cm of palpable plaque, and 3) penile bend >60° and >4 cm of palpable plaque. Groups 1, 2, and 3 received 6,000, 10,000, and 14,000 Advance Biofacture Units ([ABU]; 10,000 ABU are roughly equivalent to 0.58 mg) of CCH, respectively. A significant difference in improvement of penile curvature was observed only in Group 2 when comparing CCH with placebo. However, the response rate (in curvature and plaque size) in those with mild curvature was the highest of all severities, even with the reduced dose of CCH, suggesting that CCH could have a role in the treatment of PD patients with mild curvature. This interpretation is complicated by the concomitant stratification of plaque size, as plaque size may have accounted for some or all of the variation in response, as well as by the variation in drug dose.[23]

Objective measures of penile curvature must be contextualized to clinical meaningfulness. General consensus views 30°–45° of penile curvature as a threshold over which most males will experience some level of sexual disability. Since restoration of sexual function is a principal goal of treatment, an intervention that reduces curvature to a degree below this range will theoretically be clinically efficacious. Males in the IMPRESS trial grouped into the 30°–60° baseline curvature category had a mean baseline curvature of ~44°, and a mean reduction in absolute curvature of 14.8°. This puts their difference of means right below the threshold range at 29.2°, implying that use of CCH in patients with moderate severity curvature will often be successful in improving sexual disability. Meanwhile, males grouped into the 61°–90° category had a mean baseline curvature of ~72°, with a mean reduction in absolute curvature of 25.3°, making their difference of means land just above the threshold range at 46.7°. Hence, the utility of CCH in patients with severe curvature is likely limited in its ability to restore sexual function. This assessment also highlights the importance of reporting curvature measurements in degrees, as opposed to percent change, which requires context to derive clinical meaningfulness.

A relatively unexplored potential indication for CCH in the severe curvature subgroup is neoadjuvant CCH prior to surgical intervention. The reduction in curvature provided by CCH is probably sufficient to transition a patient who would usually have to undergo partial plaque excision and grafting into a severity zone more amenable to a less morbid tunical plication (TP) surgery. The other potential use for CCH that has been relatively unexplored is at the opposite end of the severity spectrum. Males with mild curvature (<30°), who desire an intervention for aesthetic purposes that do not warrant the risk of morbidity associated with surgery, seem to be ideal candidates for CCH therapy. Because of the currently exorbitant out-of-pocket cost, CCH needs to be FDA approved and made reimbursable for this purpose before it can be widely used. Trials highlighting the efficacy in this subgroup will be the next step in furthering this process.

Duration of disease

An abstract by Goldstein et al[24] in 2013 analyzed pooled data from the IMPRESS trials and the more recent Phase III open-label study in post hoc fashion, and stratified patients by duration of PD to assess if this affected improvement in penile curvature. Of the 776 subjects treated with CCH in these three trials, 36% presented with disease duration 1–2 years, 34% with disease duration >2 but ≤4 years, and 30% with disease duration >4 years. The analysis concluded that treatment with CCH resulted in improvement in curvature deformity regardless of duration of disease. Whether the improvements reached statistical significance compared to placebo or baseline was not reported. The authors commented that small differences were noted between subgroups, but they were not expected to be clinically meaningful.

The 2015 subgroup analysis by Lipshultz et al[22] only included IMPRESS trial data. Patients were separated into the same three groups: 1) 1 to ≤2 years, 2) >2 to ≤4 years, and 3) >4 years. A significant reduction in penile curvature compared to placebo was observed in Groups 2 and 3, but not the group with disease duration 1 to ≤2 years. Significant improvement in PD symptom bother score was only seen in the group with disease duration >4 years. The authors postulated that PD's natural history may account for the lack of significantly improved outcomes in Group 1, as patients may still be experiencing spontaneous change in penile curvature during this earlier period in the disease process.

To address this same question for patients with even shorter duration of disease, Levine stratified participants of a multi-institutional, double-blinded, randomized placebo-controlled Phase II study into two groups. In Group 1, disease duration 6 to <12 months, CCH-treated patients had an improvement in curvature compared to placebo,

but it did not reach statistical significance. In Group 2, disease duration >12 months, CCH-treated patients had a significant improvement in curvature compared to placebo. Neither group had a significant reduction in PDQ symptom bother score. Results of this study suggest that males with a longer duration of disease should expect a significant reduction in curvature with CCH treatment, but may not experience significant improvement in their symptom bother, whereas males with <1 year since disease onset cannot be definitively counseled that CCH has a significant benefit for them in penile curvature or symptom bother. An interesting secondary finding was that AE profiles were comparable regardless of PD duration. This suggests that patients can expect to experience similar side effects to CCH treatment at any point in their disease process, so optimal timing of intervention is not influenced by temporally correlated AE profiles.[25]

Disease phase at presentation

Since disease phase may have influenced the findings from subgroup analyses stratifying by duration of disease, one study chose to use it as a separate stratification parameter. This study was a post-approval analysis of CCH at a single center, which relaxed the IMPRESS inclusion criteria and allowed patients with active disease (duration of disease <12 months or subjective report of recent deformity change) to participate. Patients with both active and stable disease had significant mean curvature improvement from baseline. Although natural disease course is a potential confounding influence in active-phase patients, the stable phase subset of patients also demonstrated significant improvement in curvature, so the improvement in the active-phase subset is unlikely to be solely attributable to spontaneous disease improvement. These results raise the question of CCH's role in the treatment of PD patients with active disease, and whether ILI with CCH may in fact promote downregulation of the fibrotic process, in turn preventing or reversing disease progression. The patients in this study require a longer term follow-up to see if the changes in curvature stabilize, continue to improve, or worsen over time.[26]

Plaque calcification

The aforementioned Goldstein et al[24] abstract additionally examined plaque calcification as a potential predictor of change in penile curvature after CCH therapy. Patients with calcifications determined to interfere with injection were excluded from these trials, so degree of calcification was separated into 1) no calcification, 2) noncontiguous stippling, and 3) contiguous calcification that did not interfere with

injection. The study concluded that treatment with CCH resulted in improvement in curvature deformity regardless of the level of plaque calcification, although no data on statistical significance was reported. Group 3 was shown to have less of a percent improvement in curvature compared to the other groups, which begs the question of whether patients with calcified plaques glean comparatively less benefit from CCH therapy.

Lipshultz et al[22] also stratified by degree of plaque calcification, and used the same calcification classification system as the above study, but included only data from the IMPRESS trials. CCH-treated patients in Groups 2 and 3 did not exhibit significant improvement in percent curvature or symptom bother compared to placebo. In contrast, CCH-treated patients in Group 1 significantly improved in both primary outcome measures compared to placebo. These results suggest that CCH may not be the optimal treatment option for males with any degree of plaque calcification.

Results from past studies are conflicting with regard to typical disease course of males with calcified plaques. One retrospective review showed that a high degree of plaque calcification (Grade 3; >1.5 cm, or ≥2 plaques >1 cm) was a predictor for progression to surgery (odds ratio [OR]: 2.28), but the mere presence of calcification within a plaque did not predict likelihood of surgical intervention.[27] Another retrospective cohort study found that calcifications were strongly associated with progression to surgery (OR: 2.75) after adjusting for multiple other factors. This same study reported that patients who had surgery for PD were more likely to have plaque calcifications at their initial clinic visit (OR: 1.75).[19] Thus, although patients with high-grade plaque calcification at their first clinic visit may be better candidates for initial surgical intervention as a cost-effectiveness and patient satisfaction strategy, patients with a lesser degree of plaque calcification require more investigation as to optimal management protocol.

Baseline erectile function

Another of the stratification parameters in the Lipshultz et al[22] subgroup analysis was baseline erectile function as determined by the International Index of Erectile Function (IIEF). Patients were separated into three groups: baseline IIEF scores 1–5 (no sexual activity), 6–16 (low erectile function), and ≥17 (high erectile function). It is important to remember that patients with ED refractory to intercavernosal injection (ICI) were excluded from the IMPRESS trials, so while study participants' penile hemodynamics could not have been entirely compromised, the etiology of their poor

erectile function was not reported (ie, ED, PD, or both). When looking at primary outcomes in each of the subgroups, statistically significant reduction in penile curvature was not achieved in the subgroups with baseline IIEF scores 1–5 and 6–16 in CCH-treated patients compared to placebo. Statistically significant reduction in PDQ symptom bother score was not achieved in the subgroup with baseline IIEF scores 6–16 in CCH-treated patients compared to placebo. Patients with high erectile function significantly improved in regard to curvature and symptom bother after treatment with CCH, suggesting that patients with adequate baseline erectile function are good candidates for CCH therapy.[22] More accurately, detailing the underlying cause of these patients' poor erectile function prior to treatment, and whether it is in part attributable to PD, will be an important aspect of future studies, to identify those who will derive maximal benefit from the treatment of PD with CCH vs treatment of ED.

Plaque size

As mentioned previously, the Gelbard et al[23] study also included plaque size in its stratification scheme (see "Baseline curvature severity"). Although conclusions are difficult to draw due to confounding between CCH dose variability, differing plaque size, and varying curvature severity, this study introduces the possibility that the response rate may be inversely related to plaque size.[23]

The idea of plaque size as a predictor of PD outcomes was explored in a single-institution retrospective review (n=810) of males with PD on whom a penile duplex Doppler ultrasound (PDDU) was obtained. Not only did multivariate analysis find plaque size to be strongly correlated with ED, but the review also concluded that plaque size was a strong predictor of surgical intervention for PD treatment. This, taken in conjunction with the findings from the above study, indicates that plaque size as a predictor of response to CCH treatment warrants further investigation. Patients with large plaques may benefit from a PD treatment algorithm streamlining them to early surgery, whereas small plaque size may be an independent predictor of positive response to treatment with CCH.[28]

Age

A 2013 subgroup analysis by Hertzman et al[29] using IMPRESS trial data evaluated the effect of age on primary outcomes in CCH-treated patients and found that percent change in penile curvature and PDQ symptom bother score were improved across age groups, but no data on statistical significance was reported. Some additional interesting trends were observed. Males <45 and >75 years had the greatest improvements in PDQ symptom bother score, marking them as potential populations of interest for future studies. Males >75 years demonstrated this improvement despite achieving less than half of the improvement in percent curvature deformity change as the other age groups, suggesting a disconnect between objective change in curvature and subjective patient-perceived symptom bother, at least in older males.

In 2002, a retrospective review from Kadioglu et al[6] collected data on 307 males with PD to better understand the epidemiology and natural history of the disease and reported some interesting age-related statistics. One of their points of focus was PD's relationship with ED, and which characteristics of PD patients would predict association with ED. They found that PD patients aged >60 years are almost five times more likely to have ED refractory to intracavernosal injection with papaverine. Another reported statistic was that patients >60 years with PD for >12 months and at least one risk factor for systemic vascular disease had an 86.7% chance of refractory ED. Since the only recommended therapy for PD patients with refractory ED is inflatable penile prosthesis placement, older patients, particularly ones with long duration of PD and vascular comorbidities, may not be ideal candidates for CCH therapy. On the other end of the spectrum, this study also commented on PD considerations specific to younger patients. If a PD patient presents before age 50 years in the active phase of disease, is potent, and has at least one vascular risk factor, he has an 87.5% chance of deterioration in his PD condition. If CCH can be shown to temper PD deterioration, then young males with PD, especially if they have the other aforementioned characteristics, are ideal candidates for early initiation of CCH therapy.

Comorbid diabetes

Hertzman et al[29] also addressed the effect of concomitant diabetes on outcomes. Results showed that percent change in penile curvature and PDQ symptom bother score improved in those both with and without diabetes. The study concluded that patients respond to treatment with CCH regardless of presence or absence of concomitant diabetes.

Previous penile trauma

The Hertzman subgroup analysis additionally looked at the effect of previous penile trauma on outcomes. Results showed that percent change in penile curvature and PDQ symptom bother score improved in those both with and without previous penile injury. The study concluded that CCH is efficacious regardless of the history of penile trauma.[29]

Responsiveness to first treatment cycle

Results of a single-center retrospective review investigating the impact of the number of cycles of CCH treatment on PD outcomes were reported by Anaissie et al.[30] The study found that patients who achieved ≥20% improvement in curvature from baseline had significantly more response following the first treatment cycle compared to those who experienced <20% improvement. Based on this finding, patients could potentially be counseled on their predicted overall response to four cycles of CCH therapy based on their response to the first cycle. However, drawing conclusions is limited by the fact that only 46% of the study population completed all four cycles, and those who did not achieve ≥20% improvement in curvature underwent fewer treatment cycles compared to those who did (2.5 vs 3.6; $P<0.001$). It would be interesting to perform a subgroup analysis stratified by number of completed treatment cycles to observe if the association between ≥20% improvement in curvature and increased response to the first treatment cycle still remains. Another noteworthy finding was significant improvement in penile curvature after each treatment cycle, with the exception of the fourth. Thus, if patients are satisfied after three treatment cycles, they may consider forgoing the fourth cycle.

Baseline penile shortening or pain

In the IMPRESS trials, the only secondary endpoints of the total seven that were not significantly improved with CCH treatment were penile length and penile pain. Hence, CCH is not FDA-approved or American Urological Association-recommended for improvement in pain or length in PD patients. However, the 2015 open-label Phase III trial reported significant improvement in all seven secondary endpoints after CCH treatment, including pain and length. This discrepancy deserves further study, as patient selection for CCH monotherapy could be expanded to include PD patients whose symptomatology included penile pain or shortening. It is important to remember that a patient presenting with pain is likely still in the active phase of disease, which may affect treatment decisions (see "Disease phase at presentation"). An additional consideration for the treatment of PD patients who are highly averse to penile shortening as a side effect of PD treatment is this: although the IMPRESS trials failed to show improvement of penile length with CCH therapy, they succeeded in showing that treatment with CCH does not cause penile shortening. This finding is far from inconsequential in light of the relatively prevalent occurrence of penile shortening as a side effect of surgical intervention

for PD and should be mentioned to patients deciding between surgery and ILI with CCH.[16]

Prior treatment with ILI

Goldstein reported on the results of a Phase III open-label study of males who received placebo in the IMPRESS trials and subsequently received CCH therapy. These males experienced a mean 36.3% improvement in penile curvature deformity and a 2.4-point improvement in PDQ symptom bother score. Statistical significance of these changes compared to baseline was not reported. Absolute change in degrees of curvature was also not reported.[31] Compare these results to those of the IMPRESS trials, in which CCH-treated males had a mean 34% improvement in curvature and a 2.8-point improvement in PDQ symptom bother score. The males included in this trial reportedly experienced a mean 18% improvement in curvature and a 1.8-point improvement in PDQ symptom bother score after treatment with placebo in the IMPRESS trials. The total percent improvement in curvature and total change in PDQ symptom bother score that the males in this trial experienced, compared to their baseline before the IMPRESS trials, may demonstrate if the two cycles of ILI had an additive effect. This concept introduces a vast new set of possible treatment combinations – placebo ILI as a primer prior to CCH ILI, multiple courses of CCH ILI, rotating courses of CCH and other currently off-label ILI therapies, and so on. If any of these prove to be promising, it would extend patient selection to include males with primary CCH treatment failure, as well as present the challenge of uncovering whether various patient and disease characteristics would predict better response to one of these combinations over another.

Compliance with plaque modeling

It is believed that manual modeling of penile plaques works synergistically with enzymatic weakening from CCH to further decrease the restrictive effects of the plaque on the tunica albuginea during erection. Results from the Gelbard et al[32] study (2012), a randomized, double-blinded, placebo-controlled Phase IIb trial, hinted at the usefulness of manual penile plaque modeling therapy as an adjunct to CCH ILI. Patients were randomized into four groups to test CCH vs placebo and modeling vs no modeling. Although the difference was not significant, mean percent improvement in curvature was greater in the CCH group with modeling than the CCH group without modeling. The mean PDQ symptom bother score was significantly improved in the CCH group with modeling compared to the CCH group without modeling.

Selecting patients with the dexterity and compliance necessary to perform intercycle home modeling may enhance CCH treatment outcomes.

Atypical curvature

Patients with ventral curvature and indentation/hourglass deformity were excluded from the IMPRESS trials study population, so CCH is not FDA-approved for use in these patients. These deformities were excluded due to a theoretical risk of urethral injury and inability to objectively measure the deformity, respectively. Results of new studies addressing general safety of ILI for use in ventral curvature, as well as use of CCH specifically, have been recently published. No studies characterizing safety or efficacy of CCH ILI for use in indentation deformities are yet available.

A retrospective dual-institution study (n=35) of males undergoing ILI with interferon (21) or TP (14) for ventral curvature reported no major procedural complications with ILI therapy. Although TP had significantly better improvement in curvature, ILI therapy yielded better results in preserving or increasing penile length, which almost reached statistical significance compared to TP. Scores for the Sexual Health Inventory for Males (SHIM) were not different in intra- or inter-group analysis. However, 0% of the TP group reported improved SHIM scores after treatment, whereas 36% of males undergoing ILI therapy reported improved SHIM scores. These data provide evidence for the safety of ILI for use in ventral curvature, as well as anecdotal support for its efficacy, particularly for patients concerned about penile shortening.[33]

A separate retrospective single-institution review (n=131) of males treated with interferon ILI for PD included 21 patients with ventral curvature deformity. There were no reports of urethral damage or stricture formation. In addition, there were no differences in treatment efficacy outcomes between the patients with ventral curvature compared to all other treated patients. These results suggest that ILI can be used with equal efficacy and safety in patients with ventral curvature as in patients with dorsal and lateral curvatures.[34]

Further evidence for the safety of ILI, specifically CCH, in the treatment of ventral PD can be extrapolated from a recent animal study investigating the effect of CCH on a rat model of urethral stricture disease. Transforming growth factor beta was used to induce urethral fibrosis in 30 rats, which were then given urethral injections of CCH. Treatment with CCH was deemed safe in the animal model and was successful in reducing fibrosis and collagen expression.[35]

Finally, Milam[36] reported on the experience of offering ILI with CCH to two patients with ventral PD. After four cycles with CCH treatment, the males improved from 45° to 5°, and 30° to <10°, respectively. Neither had urethral side effects, besides mild pain and ecchymosis.

As a note on patient selection considerations for males with indentation deformities, results from Cakan et al,[37] single-center retrospective review (n=703) of males presenting with PD, may provide some insight into treatment decisions. Of all males presenting with PD, 89 had indentation deformities. The most common presenting symptom in those males was ED (69%), whereas the rest of the study population had only 55% prevalence of ED. Prevalence of diminished erectile capacity in response to injection and stimulation was significantly higher in the males with indentation deformities compared to the males with all other types of PD (46% vs 32%, respectively). Treatment for ED refractory to medication is inflatable penile prosthesis placement. Considering the paucity of data supporting the use of any noninvasive therapies for the treatment of indentation deformities, plus the high chance of these patients having concomitant ED, initial surgical intervention may be an appropriate option.

In summary, CCH has been used off-label for the treatment of patients with atypical PD in real-world practice settings.[20] However, because it is not FDA approved for use in patients with ventral curvature or hourglass deformity, it is not reimbursable by insurance and is cost prohibitive to a majority of patients. Larger, more inclusive studies must be performed before these indications will be updated.

Additional considerations

Other factors potentially affecting response to CCH therapy that have yet to be investigated include patient race, ethnicity, family history of PD, plaque number, comorbid medical ED (as proven by PDDU and/or nocturnal penile tumescence), severity of baseline disease-associated distress, sexual orientation, use of antidepressants, frequency of erections ± intercourse or masturbation during treatment course, direction of curvature, relationship status, hypogonadism, simultaneous use of other pharmacology, and various systemic vascular disease comorbidities other than diabetes. Most of the existing trials had short follow-up periods and will need to be followed into the future. Recently, a report on the original study population for the CCH in Dupuytren's contracture Phase III study was released, which described a 35% recurrence rate.[38] Similar recurrence rates in the PD population treated with CCH are feasible. Studies may then need to extend patient selection analysis to search for predictors of recurrence, as well as predictors of response to adjuvant injection therapy.

The studies included in this literature review had several shared limitations. Many were based on post hoc subgroup analysis of the IMPRESS trials data. The IMPRESS trials were not designed with the intent of adequately powering subgroup analyses, so many of the subgroups discussed here contain too small a sample size to permit valid statistical analysis of CCH efficacy, and results can only be used to develop hypotheses, not to draw conclusions. Other common limitations were lack of randomization and matched controls, lack of blinding, absence of full statistical analysis, presence of confounding factors, nonstandardized heterogeneous protocols, arbitrary and/or unclear definitions, stringent inclusion/exclusion criteria, and lack of clinically meaningful treatment outcomes. The findings from these studies may be used anecdotally to influence point-of-care treatment decisions regarding the use of CCH for PD patients, but future studies must harness increased statistical power and address these other limitations before the findings can be adopted into evidence-based guidelines. Statistical analysis of future studies will ideally include both intra- and inter-subgroup comparisons, as well as multivariate analyses to minimize the effect of confounding.

Of note, most of these analyses placed weight on improvement in curvature as the most important outcome to predict. To date, the evidence associating severity in curvature with the symptoms of PD is sparse, and even scarcer for the association between curvature severity and patient satisfaction with treatment. The validity of curvature severity thresholds as clinically meaningful treatment goals needs to be definitively proven. Completing this task in a timely manner is paramount to progression in the field, because if a reliable relationship cannot be defined between penile curvature and PD symptomatology, then a paradigm shift in measuring treatment outcomes and identifying predictors of those outcomes needs to be implemented. In the meantime, if improvement in curvature is included as an outcome, it is more useful to be reported as absolute improvement in degrees rather than percent improvement. Patient-reported outcomes, in addition to improvement in curvature, need to be included as primary outcomes in future analyses looking for predictive factors.

See Table 3 for a summary of the studies examining the various potential predictive factors for outcomes after treatment with CCH.

Table 3 Potential predictive factors for outcomes of treatment with CCH for PD

Study	Design	Stratification	Findings
Baseline curvature severity			
Lipshultz et al,[22] 2015	Subgroup analysis of IMPRESS trials data	Group 1: 30°–60° (n=318, CCH; n=174, placebo) Group 2: 61°–90° (n=83, CCH; n=37, placebo)	• Group 1: curvature improvement compared to placebo 34% vs 17%, **P<0.001** (15° vs 8°); improvement in PDQ symptom bother score compared to placebo 2.9 vs 1.9, **P=0.004** • Group 2: curvature improvement compared to placebo 35% vs 23%, **P=0.008** (25° vs 17°); improvement in PDQ symptom bother score compared to placebo 2.5 vs 1.2, P=0.071
Gelbard et al,[23] 1993	Single-center, prospective, randomized, placebo-controlled double-blinded Phase I study	Group 1: <30° and plaque <2 cm (n=7) Group 2: 30°–60° and 2–4 cm plaque (n=24) Group 3: >60° and >4 cm plaque (n=18)	• Significant improvement in curvature in Group 2 only • Response rates (in curvature and plaque size) compared to placebo were 100% vs 25% in Group 1, 36% vs 0% in Group 2, and 13% vs 0% in Group 3
n/a	Combination of data reported in IMPRESS trials and their subgroup analyses	Group 1: 30°–60° (n=318, CCH; n=174, placebo) Group 2: 61°–90° (n=83, CCH; n=37, placebo)	• Group 1 had an average baseline curvature of 44°, with a mean improvement in curvature of 15°, putting their difference of means at 29° after treatment • Group 2 had an average baseline curvature of 72°, with a mean improvement in curvature of 25°, putting their difference of means at 47° after treatment • At baseline, 38% of CCH-treated males had curvature <45°; after treatment with CCH, 75% of these males had curvature <45°
Duration of disease			
Goldstein et al,[24] 2013	Subgroup meta-analysis of data from IMPRESS trials and 2015 open-label Phase III study, including only CCH-treated males	Group 1: 1–2 years (n=280) Group 2: >2 and ≤4 years (n=266) Group 3: >4 years (n=230)	• Group 1: 29% (16°) mean improvement in curvature • Group 2: 35% (18°) mean improvement in curvature • Group 3: 39% (19°) mean improvement in curvature

(Continued)

Table 3 (*Continued*)

Study	Design	Stratification	Findings
Lipshultz et al,[22] 2015	Subgroup analysis of IMPRESS trials data	Group 1: 1–2 years (n=134, CCH; n=67, placebo) Group 2: >2 and ≤4 years (n=136, CCH; n=76, placebo) Group 3: >4 years (n=131, CCH; n=68, placebo)	• Group 1: curvature improvement compared to placebo 29% vs 24%, *P*=0.28 (14° vs 13°); improvement in PDQ symptom bother score compared to placebo 2.9 vs 2.0, *P*=0.14 • Group 2: curvature improvement compared to placebo 34% vs 17%, ***P*<0.001** (17° vs 9°); improvement in PDQ symptom bother score compared to placebo 2.6 vs 1.8, *P*=0.07 • Group 3: curvature improvement compared to placebo 40% vs 14%, ***P*<0.001** (20° vs 14°); improvement in PDQ symptom bother score compared to placebo 3.0 vs 1.6, ***P*=0.01**
Levine et al,[25] 2015	Multi-institutional, randomized, placebo-controlled double-blinded, Phase II study	Group 1: 6–12 months (n=22, CCH; n=12, placebo) Group 2: >12 months (n=78, CCH; n=22, placebo)	• Group 1: curvature improvement compared to placebo 38% vs 20%, *P*=0.08 (19° vs 9°); improvement in PDQ symptom bother score compared to placebo 2.4 vs 0.5, *P*=0.24 • Group 2: curvature improvement compared to placebo 28% vs 7%, ***P*=0.004** (15° vs 3°); improvement in PDQ symptom bother score compared to placebo 2.6 vs 0.9, *P*=0.12 • AE profiles comparable regardless of PD duration
Disease phase at presentation			
Yang and Bennett[26] 2016	Post-approval analysis of CCH at a single center	Group 1: active disease (n=12) Group 2: stable disease (n=37)	• Group 1: curvature improvement compared to baseline 20°, ***P*<0.01** • Group 2: curvature improvement compared to baseline 14°, ***P*<0.0001** • Median number of cycles for the total cohort was 3; median number of cycles for Group 1 was 2.5
Plaque calcification			
Goldstein et al,[24] 2013	Subgroup meta-analysis of data from IMPRESS trials and 2015 open-label Phase III study, including only CCH-treated males	Group 1: no calcification (n=537) Group 2: noncontiguous stippling (n=149) Group 3: contiguous calcification (n=90)	• Group 1: 35% (18°) mean improvement in curvature • Group 2: 4% (17°) mean improvement in curvature • Group 3: 27% (14°) mean improvement in curvature
Lipshultz et al,[22] 2015	Subgroup analysis of IMPRESS trials data	Group 1: no calcification (n=287, CCH; n=160, placebo) Group 2: noncontiguous stippling (n=76, CCH; n=27, placebo) Group 3: contiguous calcification (n=38, CCH; n=24, placebo)	• Group 1: curvature improvement compared to placebo 34% vs 17%, ***P*<0.001** (17° vs 9°); improvement in PDQ symptom bother score compared to placebo 2.9 vs 1.7, ***P*<0.001** • Group 2: curvature improvement compared to placebo 36% vs 26%, *P*=0.110 (18° vs 12°); improvement in PDQ symptom bother score compared to placebo 2.6 vs 1.8, *P*=0.342 • Group 3: curvature improvement compared to placebo 28% vs 20%, *P*=0.231 (14° vs 9°); improvement in PDQ symptom bother score compared to placebo 2.7 vs 2.7, *P*=0.985
Baseline erectile function			
Lipshultz et al,[22] 2015	Subgroup analysis of IMPRESS trials data	Group 1: IIEF scores 1–5 (n=16, CCH; n=6, placebo) Group 2: IIEF scores 6–16 (n=67, CCH; n=39, placebo) Group 3: IIEF scores ≥17 (n=314, CCH; n=166, placebo)	• Group 1: curvature improvement compared to placebo 28% vs 13%, *P*=0.234 (16° vs 9°); improvement in PDQ symptom bother score compared to placebo 2.9 vs 0.2, ***P*=0.026** • Group 2: curvature improvement compared to placebo 28% vs 20%, *P*=0.227 (16° vs 10°); improvement in PDQ symptom bother score compared to placebo 3.5 vs 2.9, *P*=0.408 • Group 3: curvature improvement compared to placebo 36% vs 18%, ***P*<0.001** (17° vs 9°); improvement in PDQ symptom bother score compared to placebo 2.7 vs 1.6, ***P*=0.002** • Baseline curvature was similar across all subgroups
Plaque size			
Gelbard et al,[23] 1993	Single-center, prospective, randomized, placebo-controlled, double-blinded Phase I study	Group 1: <30° and plaque <2 cm (n=7) Group 2: 30°–60° and 2–4 cm plaque (n=24) Group 3: >60° and >4 cm plaque (n=18)	• Significant improvement in curvature in Group 2 only • Response rates (in curvature and plaque size) compared to placebo were 100% vs 25% in Group 1, 36% vs 0% in Group 2, and 13% vs 0% in Group 3

(Continued)

Table 3 (*Continued*)

Study	Design	Stratification	Findings
Age			
Hertzman et al,[29] 2013	Subgroup analysis of IMPRESS trials data, including only CCH-treated males	Group 1: <45 years (n=29) Group 2: 45–55 years (n=114) Group 3: 56–64 years (n=196) Group 4: 64–74 years (n=60) Group 5: ≥75 years (n=2)	• Group 1: 39% (18°) mean improvement in curvature; mean improvement of 4.7 in PDQ symptom bother score • Group 2: 31% (16°) mean improvement in curvature; mean improvement of 2.8 in PDQ symptom bother score • Group 3: 36% (18°) mean improvement in curvature; mean improvement of 2.7 in PDQ symptom bother score • Group 4: 32% (16°) mean improvement in curvature; mean improvement of 2.6 in PDQ symptom bother score • Group 5: 15% (7°) mean improvement in curvature; mean improvement of 5.5 in PDQ symptom bother score
Comorbid diabetes			
Hertzman et al,[29] 2013	Subgroup analysis of IMPRESS trials data, including only CCH-treated males	Group 1: diabetes Group 2: no diabetes	• Group 1: 34% (17°) mean improvement in curvature; mean improvement of 2.7 in PDQ symptom bother score • Group 2: 34% (17°) mean improvement in curvature; mean improvement of 2.9 in PDQ symptom bother score
Previous penile trauma			
Hertzman et al,[29] 2013	Subgroup analysis of IMPRESS trials data, including only CCH-treated males	Group 1: history of penile trauma (n=129) Group 2: no history of penile trauma (n=422)	• Group 1: 35% (18°) mean improvement in curvature; mean improvement of 3.0 in PDQ symptom bother score • Group 2: 34% (17°) mean improvement in curvature; mean improvement of 2.8 in PDQ symptom bother score
Responsiveness to first treatment cycle			
Anaissie et al,[30] 2016	Single-center retrospective review	Group 1: ≥20% improvement in curvature Group 2: <20% improvement in curvature Total n=78	• Group 1 had a significantly greater response after the first treatment cycle compared to Group 2 (17° vs 6°, *P*<0.001) • Within the total cohort, significant improvement in curvature was experienced after each treatment cycle except the fourth cycle
Baseline penile shortening or pain			
n/a	IMPRESS trials	CCH, n=401 Placebo, n=211	• CCH-treated male's increase in length compared to placebo (0.4 cm vs 0.2 cm, *P*=0.0408) • CCH-treated male's improvement in PDQ pain score compared to placebo (4.4 vs 4.3, *P*=0.9672)
n/a	2015 open-label Phase III study	Males included in length calculations, n=238 Males included in pain calculations, n=114	• Compared to baseline, participants had a significant increase in length (0.4 cm, *P*<0.05) • Compared to baseline, participants had a significant improvement in PDQ pain score (5.3, *P*<0.05)
Prior treatment with ILI			
Goldstein et al,[31] 2015	Open-label Phase III study of males who received placebo in IMPRESS trials	n=189	• Males in this study had 36% mean improvement in curvature and mean improvement of 2.4 in PDQ symptom bother score • These same males had 18% mean improvement in curvature and mean improvement of 1.8 in PDQ symptom bother score after treatment with placebo at conclusion of IMPRESS trials • Compare these values to the averages from CCH-treated males in the IMPRESS trials: 34% mean improvement in curvature and mean improvement of 2.8 in PDQ symptom bother score
Compliance with plaque modeling			
Gelbard et al,[32] 2012	Randomized, placebo-controlled, double-blinded Phase IIb study	Group 1: CCH + manual modeling (n=54) Group 2: CCH − manual modeling (n=55)	• Improvement in curvature in Group 1 compared to Group 2: 32% vs 27%, *P*>0.05 • Improvement in PDQ symptom bother score in Group 1 compared to Group 2: 3.6 vs 1.5, *P*<0.05
Atypical curvature			
Milam[36] 2016	Report on ILI with CCH for ventral curvature	n=2	• Patient 1 improved from 45° pretreatment to 5° after four cycles of CCH • Patient 2 improved from 30° pretreatment to 5°–10° after four cycles of CCH • No reported urethral side effects

(*Continued*)

Table 3 (*Continued*)

Study	Design	Stratification	Findings
Predictors of patient and partner satisfaction			
Traore et al,[39] 2016	Single-institution retrospective review	Group 1: satisfied patients (n=16) Group 2: unsatisfied patients (n=8) Group 3: satisfied FSPs (n=17) Group 4: unsatisfied FSPs (n=7)	• No significant differences were found between Groups 1 vs 2 or Groups 3 vs 4 when stratifying by age, disease duration, baseline curvature, curvature direction, # cycles of therapy, mean change in curvature, ≥20% improvement in curvature, mean change in IIEF score, presence of treatment complications, or partner pain with intercourse • 44% of Group 3 reported a history of penile trauma, compared to 0% of Group 4 (*P*<**0.05**) • 18% of Group 3 reported partner glans hypoesthesia after treatment, compared to 71% of Group 4 (*P*<**0.05**) • 100% of Group 3 was able to have intercourse after treatment, compared to 71% of Group 4 (*P*<**0.05**)

Notes: All numerical values except PDQ scores rounded to the nearest whole number. Statistical significance is indicated by bold *P*-values. Data from several studies.[8,11,22,25,30–32,34,35,38–44]

Abbreviations: CCH, collagenase *Clostridium histolyticum*; PD, Peyronie's disease; IMPRESS, Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies; AE, adverse effect; PDQ, Peyronie's Disease Questionnaire; IIEF, International Index of Erectile Function; ILI, intralesional injection; FSP, female sexual partner; n/a, not available.

Patient perspectives

Although PD can have a significant impact on quality of life, it is not life-threatening and its effects vary by individual, so seeking treatment is at the patient's discretion. Marketability and success of treatment options are consequently heavily influenced by patient satisfaction. The PD literature's assessment of contributors to and predictors of patient satisfaction with CCH treatment is meager. Another largely uninvestigated topic is the effect of PD on the sexual partners of males with PD. Their satisfaction with treatment of their partners' disease likely plays a role in the patient's satisfaction. An additional element in patient outlook on treatment with CCH is the cost, particularly for patients using it off-label. Elucidating the players contributing to patient satisfaction with CCH treatment will, in turn, help to preemptively identify which patients are more likely to be satisfied with treatment, and thus can assist in patient selection and making management recommendations. A few studies exist that explore the factors influencing patient perspective on CCH.

Patient-reported outcomes

Traore et al[39] performed a retrospective single-institution study of males treated with CCH for PD that gathered data on predictors of patient satisfaction. Twenty-four of the 78 patients who were contacted agreed to participate in a phone survey employing a binary answer modality to answer questions about ability to have intercourse and satisfaction with treatment. After treatment, 22 (92%) males were able to have sex, up from 16 (67%) before treatment. When asked if they were satisfied with treatment and if they would repeat it, 16 (67%) answered "yes". No statistically significant differences were found between satisfied and unsatisfied patients in regard to baseline patient characteristics of age, history of penile trauma, duration of PD, pretreatment curvature, direction of curvature, and number of cycles of therapy. In addition, no statistically significant differences were found between satisfied and unsatisfied patients in regard to the following treatment outcomes: mean change in curvature, ≥20% improvement in curvature, mean change in IIEF score, presence of treatment complications, ability to have intercourse, partner pain with intercourse, and glans hypoesthesia. These findings indicate that achieving patient satisfaction may be more complicated than improving physical symptoms alone, and efforts need to be made to identify other possible markers of satisfaction. This may require the use of subjective data collection methods, such as focus group interviews with PD patients.

The global assessment of PD (GAPD), one of the measurement tools used in the IMPRESS trials, is a rating scale that asks a subject to gauge the overall change in symptoms and effects of PD on his life after treatment. The scale ranges from −3 (much worse) to 3 (much improved). Using IMPRESS trial data, Hellstrom et al[40] analyzed the relationship between penile curvature measurements and GAPD response. Positive response to the GAPD (score ≥1, improved in a small but important way) was reported in males achieving penile curvature ≤45°, which equated to ≥25.5% curvature improvement. This accounted for 75% of the study population. As posttreatment penile curvature decreased, GAPD scores improved accordingly. This is an important association, as it proposes an inverse linear relationship between degrees of curvature and patient-reported assessment of treatment impact. This study is limited by the fact

that it scored all negative GAPD ratings as 0, so results are falsely weighted toward positive scores. Inclusion of negative scores into the analysis is needed for a more accurate assessment of posttreatment degree of penile curvature's ability to predict GAPD score.

Results from a single-institution prospective open-label study (n=27) of males receiving CCH for PD were reported by Ziegelmann et al.[41] Some of this study's protocol differed from the IMPRESS trials; patients with calcified plaques were included, disease stability was defined as 3+ months without symptom change (but did not require 12 months of disease duration), a different penile modeling procedure was used, and daily penile traction device usage was encouraged. The mean percent change in curvature was 38% (23°). This study also collected and analyzed several additional patient-reported outcomes: 88% of patients reported subjective improvement in curvature after four treatment cycles, 81% perceived CCH therapy as meaningful, 57% said CCH treatment negated a need for surgery, and 33% endorsed improved penile sensitivity. Fifty-two percent of those with baseline inability to have intercourse reported restoration of penetration. Patients were also asked to subjectively assess their perceived percentage improvement in penile curvature after each treatment cycle; the reported value increased compared to baseline after all cycles. It would be interesting to compare these subjective values to the objective data. Results of this study indicate that there is a large overlap between patients endorsing meaningfulness of CCH therapy and those perceiving subjective improvement in curvature, but the correlation and dependence between these two patient-reported outcomes remains undefined. It also indicates that even if patients perceive a change in curvature, it is not necessarily meaningful to them. Potential other contributors to meaningfulness are negation of need for surgery, improved penile sensitivity, and restoration of penetrative sexual ability, but none of these is solely responsible for a meaningful treatment outcome.

Coyne et al[42] sought to assess the PDQ's responsiveness to objective treatment outcomes using data from the IMPRESS trials. Analysis revealed that a 20%–50% change in penile curvature after treatment correlated with significant improvement in two of three PDQ domains: 1) symptom bother and 2) psychological and physical symptoms. These results were even more pronounced in the patient subset achieving >50% reduction in curvature. The responsiveness of the PDQ to absolute change in degrees of curvature was not assessed. This study lends support to a positive association between improvement of curvature and improvement of PD

symptoms and their bother. It also examined the PDQ's correlation with GAPD responses. Significant changes in PDQ score were observed between almost all the GAPD ratings, speaking to the PDQ's correlation with patient-reported overall effect of treatment on PD symptoms. However, the PDQ is limited by its intercourse-centric focus, so the impact of CCH treatment on patient satisfaction and self-perception unrelated to sexual performance is not assessed. Whether improvement in PDQ score is a predictor of patient satisfaction with treatment is yet unknown.

Female partner considerations

Traore et al's[39] study also assessed female sexual partner (FSP) satisfaction and its predictors. Of 24 FSPs, 17 (71%) were satisfied with treatment and said they would repeat it. Several predictors of FSP satisfaction were identified. A positive history of penile trauma was reported in 44% of satisfied FSPs, compared to 0% of unsatisfied FSPs. A proposed explanation for this finding was that females feel responsible for the past sexual trauma, and their guilt is relieved when their partners undergo treatment, contributing to overall satisfaction. Of satisfied FSPs, only 18% reported partner glans hypoesthesia following treatment, whereas 71% of unsatisfied FSPs' partners had posttreatment glans hypoesthesia. This may be a reflection of FSP's happiness with a more pleasurable sexual experience for their partner. Finally, 100% of satisfied FSPs were able to have intercourse after treatment, vs only 71% of unsatisfied FSPs. No statistical significant differences between satisfied and unsatisfied FSPs were observed in regard to patient baseline characteristics of age, duration of PD, pretreatment curvature, direction of curvature, or number of treatment cycles. Likewise, no differences were observed in regard to mean change in curvature, ≥20% improvement in curvature, mean change in IIEF score, presence of treatment complications, or partner pain with intercourse. Of note, six FSPs (25%) had pain with intercourse prior to therapy, which decreased to four (17%) after CCH therapy.

A different set of questions was posed to FSPs as part of an open-label Phase III study (n=189) of CCH for males who received placebo in the IMPRESS trials. Results were reported by Goldstein et al[31] and included responses from 30 of the patients' FSPs. They were asked to complete the Female Sexual Function Index (FSFI), as well as an investigational 12-question PDQ for FSPs (PDQ-FSP) adapted from the male's PDQ. The FSFI is separated into six scales (desire, arousal, lubrication, orgasm, satisfaction, and pain), and FSPs reported improvement in all six scales, as well as

full scale total scores. Results from the PDQ-FSP indicated FSP-perceived improvement in partner PD symptoms and female bother by partner's PD. Whether these improvements were significant was not reported. Finally, FSP sexual dysfunction, defined as FSFI total score of <26.55, decreased from 75% at baseline to 33% after partner treatment.

Cost

The only existing cost analysis was performed by Cordon et al,[43] which used a decision tree model and sought to evaluate the cost-effectiveness of CCH compared to TP surgery. The study defined success as <30° posttreatment penile curvature, in accordance with general belief that curvature above this severity may be intercourse-prohibitive. Analysis used data from published literature to calculate the probability of success of CCH treatment stratified by curvature severity (30°–60° vs 61°–90°). The reported probability of success for each group was 45.9% and 11.9% for the 30°–60° and 61°–90°, respectively. Cost of 7.2 injections was used in calculations, which is the average number of injections per patient according to the pooled safety analysis.[14] The probability of success of TP was reported as 90% regardless of baseline curvature severity. It was assumed that 50% of all injection failures would proceed to secondary TP, and all failed plications would undergo repeat plication. Cost of medications, office visits, facility and surgical fees, and predicted cost of complications, averaged from multiple institutions, were included in total cost calculations. Per patient plication cost was calculated as US$2,763, and per patient injection cost was $25,159. In sensitivity analyses, no increase in efficacy of CCH accomplished cost-equivalence. Like many other studies on CCH, this study's definition of success is a limitation, as it uses only objective measurement of curvature, not accounting for patient-reported outcomes. It is also unclear if the assumption that 50% of failed injections proceed to surgery is anecdotal or evidence-based. Plus, the costs contributing to cost calculations are not clearly defined. Despite limitations, this study has important implications from a patient's perspective, especially if cost of CCH is not covered by his insurance. Plus, the importance of correct patient selection is essential to avoid ineffective use of such a costly medication.

Confounders of patient satisfaction

A potential explanation for the lack of significant correlation between improvement in penile curvature and patient satisfaction in studies of males receiving CCH for PD is the presence of confounders. PD bother seems to be the summation of penile curvature deformity, perceived penile

shortening, and pain during intercourse.[11] Although CCH has consistently proven to be efficacious in reducing penile curvature, its effect on penile pain and length are unclear. In the IMPRESS trials, pain and length were not significantly improved compared with placebo. It is possible that multimodality treatment may reduce these confounding effects and improve patient satisfaction with CCH therapy. Traction therapy for length, nonsteroidal anti-inflammatory drugs for pain, and counseling on alternate methods for achieving sexual satisfaction given the patient's symptoms are some potential adjunctive therapies. Another potential confounder is concomitant depression. Use of a validated depression questionnaire in future CCH trials may help with assessing depression's influence on primary treatment outcomes.[44] One more important consideration in achieving patient satisfaction is patient expectations. Providing thorough education that emphasizes realistic outcomes is essential for preventing patient disappointment with CCH treatment.

Future studies are needed to further decipher what predicts a patient's satisfaction with CCH treatment for PD, so that providers can better select for ideal candidates.

Conclusion and future directions

Treatment of PD with CCH is efficacious and safe, but patient selection for this therapy is yet to be optimized. Definitive recommendations regarding ideal candidates for CCH treatment are difficult to make using the currently available data on predictors of positive or negative patient response to treatment. Ultimately, this review highlights the enduring need for well-designed clinical studies that include a large enough population to allow for high-powered subgroup analysis, or studies that look at potential predictive factors independently, plus studies that include previously excluded patient population subsets. Particular attention should be paid to males in the active phase of disease, as effective treatment in this group may halt disease progression and prevent clinically significant curvature from ever forming, as well as males with mild curvature. The field continues to want for a unifying consensus statement on standard study methodology, patient assessment, and outcome reporting. Efforts need to be made to choose clinically meaningful treatment outcomes that correlate with patient satisfaction, whether they be objective measurements or patient-reported outcomes.

Disclosure

Wayne Hellstrom was the principal investigator for the IMPRESS I and II trials. He is also an advisor and serves

on a speaker's bureau for Endo Pharmaceuticals. All other authors report no conflicts of interest in this work.

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Supplementary materials

Problem	None	Mild	Moderate	Severe	Very severe
Q1. Concern about damaging penis while having vaginal intercourse	0	1	2	3	4
Q2. Bending or collapsing of penis while having vaginal intercourse	0	1	2	3	4
Q3. Trouble inserting erect penis into partner's vagina	0	1	2	3	4
Q4. Difficulty with some positions that you used to enjoy when having vaginal intercourse	0	1	2	3	4
Q5. Awkwardness with some positions that you used to enjoy when having vaginal intercourse	0	1	2	3	4
Q6. Discomfort with some positions that you used to enjoy when having vaginal intercourse	0	1	2	3	4

Figure S1 Domain 1 – psychological and physical symptoms.

Q7. In the LAST 24 HOURS, how much pain or discomfort have you felt in your penis when it was not erect? please answer for the **LAST 24 HOURS** only.

No pain or discomfort   **Extreme pain or discomfort**

0 1 2 3 4 5 6 7 8 9 10
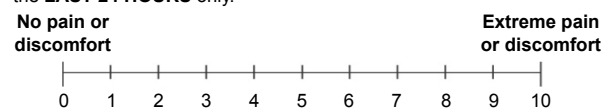
Q8. Thinking about the last time were erect, how much pain or discomfort did you feel in your penis when it was erect? please answer for the **LAST TIME YOU HAD AN ERECTION.**

No pain or discomfort   **Extreme pain or discomfort**

0 1 2 3 4 5 6 7 8 9 10

Q9. Thinking about last time you had vaginal intercourse, how much pain or discomfort did you feel in your penis when having vaginal intercourse? please answer for the **LAST TIME YOU HAD VAGINAL INTERCOURSE.**
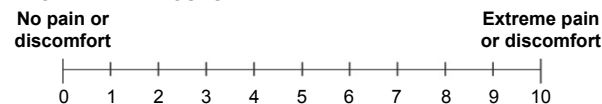
No pain or discomfort   **Extreme pain or discomfort**

0 1 2 3 4 5 6 7 8 9 10

Figure S2 Domain 2 – penile pain.

Rate the following questions as "0 – not at all bothered", "1 – a little bit bothered", "2 – moderately bothered", "3 – very bothered", or "4 – extremely bothered"
- Thinking about the last time you had an erection, how bothered were you by any pain or discomfort you may have felt in your erect penis?
- Thinking about the last time you looked at your erect penis, how bothered were you by the way your penis looked?
- Thinking about the last time you had or tried to have vaginal intercourse, how bothered were you by your Peyronie's disease?
- How bothered are you with having vaginal intercourse less often?

Figure S3 Domain 3 – symptom bother.