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Patient Reported Outcomes from a Single-center Prospective Post-marketing study on Collagenase Clostridium Histolyticum Injections for Peyronie's Disease

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ABSTRACT

The aim of this study was to evaluate patient reported outcomes of Collagenase Clostridium histolyticum (CCHi) for Peyronie's Disease. Patients treated with 2-4 cycles of CCHi between 01/2016-08/2018, were asked to fill out the "bother domain" of the Peyronie's Disease Questionnaire (PDQ) at scheduled appointments for injections. CCHi cycles involved 2 injections (0.58mg) separated by 48-72 hours. During the study 34 patients were treated, 7 patients were excluded due to incomplete baseline values. Mean PDQ bother domain baseline scores was 11.1 (2.6). ANOVA demonstrated statistically significant effects of injections ($p<0.001$) with a decrease in PDQ bother domain scores 6 weeks after the 1st cycle (9.9 (3.3), $p=0.013$), 6 weeks after the 2nd cycle (8.2 (4.0), $p=0.009$) and 6 weeks after the 3rd cycle (6.5 (3.6), $p<0.001$). After 2-4 cycles of CCHi treatment patients reported changes in penile curvature as "Worse" (0), "No Change" (2), "Little decrease" (10), Decrease (10) and "Significant decrease" (4). After completion of CCHi treatment 82% of patients still reported that vaginal intercourse was difficult or impossible. Patients with Peyronie's Disease undergoing CCHi treatment reported statistically significant decreases in PDQ bother domain scores. However, most patients still report difficulty with intercourse after treatment.

INTRODUCTION

Peyronie's Disease is considered a wound-healing disorder causing formation of a collagen plague in the tunica albuginea of the penis subsequently leading to deformities including penile shortening, abnormal penile curvature and possibly subsequent erectile dysfunction (Mulhall, Schiff, & Guhring, 2006; Smith, Walsh, Conti, Turek, & Lue, 2008). Abnormal penile curvature is highly prevalent in patients diagnosed with Peyronie's Disease and depending on the severity of the curvature sexual intercourse is often difficult and unpleasant (Gelbard, Hellstrom, et al., 2013; Smith et al., 2008). Furthermore, the curvature itself and dissatisfactory intercourse may have a major psychological impact on patients and treatment is vital to increase patient's sexual health and quality of life (Nelson et al., 2008; Smith et al., 2008).

Historically, the only effective treatment for penile curvature caused by Peyronie's Disease has been surgery, which today remains the gold standard (Yafi et al., 2018). In 2013, the U.S. Food and Drug Administration approved the use of Collagenase Clostridium Histolyticum injections (CCHi) given intralesionally. The approval was based on the Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies (IMPRESS) trials (Gelbard, Goldstein, et al., 2013) demonstrating that CCHi significantly reduces penile curvature. IMPRESS I and II included 832 patients and after 4 cycles of CCHi penile curvatures were reduced by a mean of 34% compared to a mean of 18.2% in the placebo group ($p < 0.0001$). Following the approval more studies were conducted based on the IMPRESS protocol showing both positive and inconclusive results of CCHi (Wymer, Ziegelmann, Savage, Kohler, & Trost, 2018; Yafi et al., 2018; Yang & Bennett, 2016). The main outcome measure in most of these studies is penile curvature measured as the angle between the proximal shaft and the distal part of the penis. Although penile curvature is considered an objective treatment parameter for evaluating CCHi treatment, curvature reduction does not always align with patient satisfaction after treatment (Tsambarlis & Levine, 2019). Other parameters, e.g. pain during sexual intercourse, can be more important to patients. These parameters are assessed in the Peyronie's Disease questionnaire (PDQ) bother domain which consists of 4 scored items and 2 yes/no questions including questions regarding vaginal intercourse and the patient's perception of his penis. The PDQ bother score ranges from 0-16 and a higher score indicates greater bother severity. The aim of this prospective non-randomized clinical study was to evaluate patient reported outcomes (PROs) of CCHi for Peyronie's Disease in a post-marketing real-life clinical setting.

MATERIAL AND METHODS

1. Patients

Institutional review board approval was obtained to review charts of all men between January 2016 and August 2018 at the University of **** Department of Urology who underwent treatment with CCHi. Patients with dorsal, dorsolateral or lateral penile curvatures between 30-90 degrees eligible for CCHi treatment were asked to complete

the PDQ prior to each series of injections. According to health insurance policies, most patients were previously administered oral therapies, such as Vitamin E and Pentoxifylline and/or other therapies, such as topical Verapamil, without success.

Data on enrolled patients was recorded into a de-identified database. Protected health information about the patients was not recorded into the database in agreement with safe harbor of data collection. Furthermore, only researchers with proper training were permitted to investigate patient records. Patients charts were reviewed to register date of birth, duration of Peyronie's Disease and any history of penile trauma during sexual activity, as well as other relevant clinical information that could impact the administration of CCHi, such as use of anticoagulants. At the baseline visit when CCHi treatment was discussed, the patient's penile curvature was measured via a patient-provided photograph or after prostaglandin injection in clinic. The baseline visit is defined as the visit of the first CCHi treatment. Thus, baseline data represents the situation just prior to the first injection.

2. Treatment protocol and data collection

Inclusion criteria for the study were men with a dorsal, dorsolateral or lateral penile curvatures between 30-90 degrees, who were not anticoagulated with medication other than aspirin, and for whom insurance coverage for CCHi could be confirmed. Exclusion criteria included men with plaques and curvature less than 30 degrees, men on active anticoagulation, and men with dorsal, dorsolateral or lateral penile curvatures between 30-90 degrees for whom insurance authorization could not be obtained.

The CCHi protocol used in this study consisted of treatment with 1-4 cycles of CCHi, as described in the package insert. Each CCHi cycle involved 2 injections (0.58mg) separated by 48-72 hours. Cycles were separated by at least 6 weeks. After a minimum of 48 hours after the second injection of the series, a penile modelling session was scheduled. Patients were instructed how to perform the modeling at home and provided the company instructions on specific technique including stretching and manual modelling.

At scheduled appointments for injections patients were asked to fill out the "bother domain" of the Peyronie's Disease Questionnaire (PDQ) along with a consent form for treatment, prior to injection treatment. Changes in their penile curvature were categorized as "worse", "no change", "little decrease", "decrease", "significant decrease". Patient charts were re-examined in October 2019 to record if any patient had surgery after CCHi treatment.

3. Statistics

Statistical analyses were performed with the use of computing environment R (), Vienna, Austria). A one-way repeated measure analysis of variance (ANOVA) was conducted to evaluate the null-hypothesis that there is no change in patients' PDQ scores following injections. Pairwise comparisons of PDQ scores at baseline and after each cycle were performed using paired samples t-test. To account for multiple comparisons the Bonferroni correction was applied setting the significance level to 0.05/3 = 0.017.

RESULTS

A total of 34 patients were enrolled in the study between January 2016 and August 2018. Due to incomplete baseline values 7 patients were excluded from analysis. Baseline- and clinical characteristics of the 27 patients who completed the treatment are shown in table 1. Four of these patients had a history of penile trauma while the etiology of Peyronie's Disease in the remaining patients was unknown. Five patients completed 2 CCHi cycles, 4 patients had 3 CCHi cycles and 18 patients had 4 cycles of CCHi (Figure 1). Median follow-up time was 6 months (range 2-12) defined as the last documented visit in the clinic after the 1st cycle of CCHi treatment. However, patient charts were reviewed up to 46 months after the 1st cycle of CCHi to record if any patient had surgery after CCHi. Apart from mild bruising after injections complications included 1 patient who reported increased plaque size but no increase in curvature, 3 patients with swelling and ecchymosis and 1 patient with moderate bruising and tenderness. No tunical ruptures were reported.

The mean baseline PDQ bother domain scores was 11.1 (2.6) (Table 2). The result of the ANOVA indicated statistically significant effect of injections ($p < 0.001$). Follow up pairwise comparisons using paired samples t-test indicated statistically significant differences between the PDQ scores at baseline and 6 weeks after the 1st cycle ($p = 0.013$), between baseline and 6 weeks after the 2nd cycle ($p = 0.009$) and between PDQ scores at baseline and PDQ scores at 6 weeks after the 3rd cycle ($p < 0.001$) respectively (Table 2, Figure 1 and Figure 2). In addition, 6 weeks after the 1st cycle all patients answered "yes" to PDQ question 3 ("Does your Peyronie's Disease make having vaginal intercourse difficult or impossible?"), 6 weeks after the 2nd cycle 15/18 answered "yes" and 6 weeks after the 3rd cycle 14/17 answered "yes" (Table 2). After 2-4 cycles of CCHi patients reported changes in penile curvature as "Worse" (0), "No Change" (2), "Little decrease" (10), "Decrease" (10) and "Significant decrease" (4). The 2 patients who reported "No Change" in penile curvature after CCHi treatment proceeded with surgery. One patient had plaque incision and collagen fleece grafting with good results, but reported worsening of erectile dysfunction after the surgery. The other patient had plication and an inflatable penile prosthesis implantation with good results. Finally, a patient reporting "Decrease" in curvature after CCHi treatment had a plication and afterwards complained of penile shortening. No unusual difficulties were experienced with any of the surgeries after CCHi treatment.

DISCUSSION

This study demonstrated that CCHi treatment in a real-life environment resulted in a statistically significant decrease in PDQ bother scores 6 weeks after the 1st cycle, the 2nd cycle, and the 3rd cycle when compared to baseline scores. Further, mean PDQ bother scores after completed CCHi treatment were below 9, which has been suggested as a cut-off for distinguishing clinically significant bother. When asked how their penile curvature had changed almost all patients reported a decrease in curvature, no patients reported worsening, and only 2 patients reported no change. However, 14 of 17 patients answered "yes" to the PDQ question 3 ("Does your Peyronie's Disease make having vaginal intercourse difficult or impossible?") 6 weeks after the 3rd cycle whereas at baseline all patients answered "yes" (n =

27). In addition, 3 patients had Peyronie's Disease surgery after CCHi treatment. These results are somewhat conflicting indicating overall positive effect of CCHi treatment on patients' penile curvature and bother, but little improvement in the ability to have vaginal intercourse.

Patients were offered a follow-up appointment after the 4th cycle if they were not satisfied; these appointments were either never scheduled by the patient or cancelled, explaining why data was not collected after the final series of injections. In addition, some patients were satisfied with the results during the treatment course and cancelled remaining cycles while others did not return for treatment without giving an explanation. No patient cancelled treatment due to adverse events.

Post-approval studies investigating the efficacy of CCHi treatment have demonstrated similar results to the ones presented in this study regarding PDQ bother domain scores. In 189 men, Goldstein et al (Goldstein et al., 2017) reported a reduction in PDQ bother domain score of 2.4 points (6.3 at baseline to 3.9 after treatment) and patients experienced a mean 36.3% curvature reduction after 4 cycles using the IMPRESS protocol. Yafi et al [(Yafi et al., 2018)] demonstrated in 18 patients that PDQ bother domain score decreased by 7 points (9.9 at baseline to 3.9 after treatment) and a curvature reduction of 34.4% with CCHi treatment using the IMPRESS protocol. Both studies concluded that CCHi is a safe and viable non-surgical option for treatment of Peyronie's Disease. The IMPRESS trials originally demonstrated a statistically significant improvement ($p = 0.0037$) in PDQ bother domain score after CCHi treatment (from 7.5 at baseline to 4.6 after treatment) (Gelbard, Goldstein, et al., 2013). These studies and the majority of other CCHi studies mainly focus on penile curvature reduction and frequently demonstrate positive results in this regard. However, objective and subjective measures in patients with Peyronie's Disease do not always align (Tsambarlis & Levine, 2019). Patient expectations and satisfaction as subjective parameters will not necessarily be reflected by objective parameters highlighting the important role of PROs in evaluation of Peyronie's Disease.

Few studies specifically investigate PROs such as patient' and partner satisfaction with CCHi treatment. Ziegelmann et al. (Ziegelmann et al., 2016) investigated 69 patients undergoing CCHi treatment with 31 completing all 4 cycles. The study focused on PROs as well as penile curvature improvement. The penile curvature was measured in 27 of the patients who completed all 4 cycles and 20 of those men experienced a curvature improvement of 20% or more. Furthermore 8 out of the 27 patients reported that the treatment restored their ability to have penetrative intercourse. In comparison we found that only 3/17 were not bothered by their Peyronie's Disease when having vaginal intercourse. Anaissie et al. (Anaissie, Yafi, Traore, Sikka, & Hellstrom, 2017) investigated patient and partner satisfaction after CCHi treatment for Peyronie's Disease. Using a self-designed satisfaction questionnaire 16/24 patients reported overall satisfaction with the treatment and 17/24 female sexual partners were satisfied with the treatment. They found an overall post-treatment mean curvature reduction of 16 degrees (SD 10.7). Importantly, satisfaction was associated with the ability to have sexual intercourse and not curvature reduction.

In general, a penile curvature of <30 degrees is believed not to cause partner discomfort and wont inhibit penetrative intercourse (Ralph et al., 2010). However, few CCHi studies report a final mean penile curvature of <30 degrees, while patients might be satisfied and less bothered by the curvature after CCHi treatment (Gelbard, Goldstein, et al., 2013;

Russo et al., 2018; Tsambarlis & Levine, 2019). This suggests that patient satisfaction is tied to other factors than curvature reduction. Serefoglu et al. (Serefoglu et al., 2017) performed a post hoc analysis of the IMPRESS trials data and assessed 608 patients' PDQ scores. They demonstrated that pain during intercourse had the greatest impact on PDQ bother domain score ($p < 0.0001$). Pain was present in 61% of the men during vaginal intercourse and 53.1% experienced pain when the penis was erect. The authors suggested that pain treatment may be practically beneficial for patients with Peyronie's disease. Pain during intercourse might partly explain why the majority of patients in our study still reported vaginal intercourse as being difficult or impossible after CCHi treatment. On the contrary it might be that softening of the plaque by CCHi, that is not measured by a reduction in curvature, is felt by the patient during intercourse and provides some pain relief. In combination with a CCHi induced reduction in penile curvature, this might explain the satisfaction experienced by Peyronie's Disease patients treated with CCHi. However, it does not seem that CCHi treatment makes vaginal intercourse free from discomfort as 82% of patients still reported that vaginal intercourse was difficult or impossible after CCHi treatment. Thus, patients should be informed that although they can expect bother relief and reduction in curvature, the treatment will likely not make vaginal intercourse completely free for discomfort.

The main limitation of our study is the relatively small sample-size for a single institution and the lack of a control group. Sample size was restricted due to the limitations of commercial insurance coverage, which also indicated a more homogeneous sample in terms of socioeconomic status. To have CCHi treatment covered by insurance patients had to be previously treated with oral therapies, such as Vitamin E and Pentoxifylline and/or other therapies, such as topical Verapamil. This might have prolonged the history of the disease and could potentially have an impact on results. However, our prospective non-randomized clinical study represents a real-world post-marketing setting focusing on PROs that are important to patients treated for Peyronie's Disease. Further, a strength of the study is that patients were followed up to assess if they had surgery performed after CCHi treatment.

In conclusion, patients with Peyronie's Disease treated with CCHi report statistically significant decreases in PDQ bother domain scores and most patients report a decrease in penile curvature after treatment. However, the majority of patients still report difficulty with vaginal intercourse after CCHi treatment.

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LEGENDS

Figure 1: Single patient's PDQ scores (y-axis) at baseline and 6 weeks after the 1st, 2nd and 3rd CCHi cycle

Figure 2: Boxplot of PDQ scores at baseline and 6 weeks after the 1st, 2nd and 3rd CCHi cycle.

Table 1: Clinical characteristics of patients treated with Collagenase Clostridium Histiolyticum injections

Table 2: Treatment outcomes of patients treated with Collagenase Clostridium Histiolyticum injections

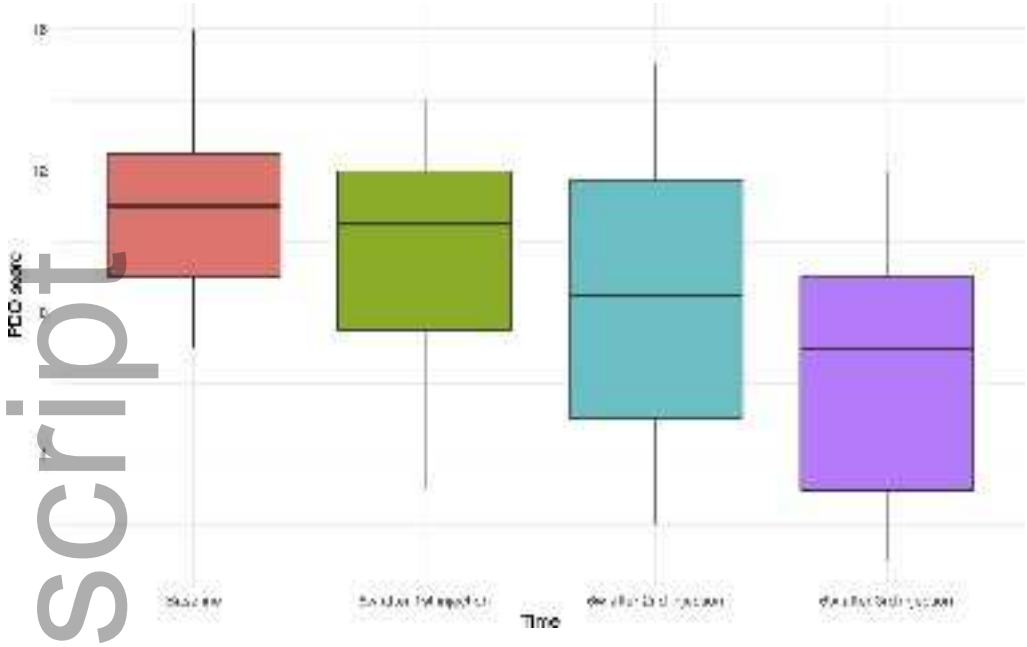
Table 1: Clinical characteristics of patients treated with Collagenase Clostridium Histiolyticum injections	
Age (years)	
mean ± SD	60 ± 9
median (range)	62 (38-74)
Duration of Peyronie's Disease (months)	
mean ± SD	26 (28)
median (range)	14 (4-108)
History of penile trauma	
n (%)	4 (15)
Pre-treatment curvature degree	
mean ± SD	56 ± 20
median (range)	45 (30-90)
30-60° n (%)	19 (70)
61-90° n (%)	8 (30)
Pre-treatment curvature direction	
Dorsal n (%)	22 (82)
Dorso-lateral n (%)	2 (7)
Lateral n (%)	3 (11)

Table 2: Treatment outcomes of patients treated with Collagenase Clostridium Histiolyticum injections					
	Baseline	6w after 1st cycle	6w after 2nd cycle	6w after 3rd cycle	After 1-4 cycles
PDQ Score*					
n	27	26	18	17	-
mean ± SD	11.1 ± 2.6	9.9 ± 3.3	8.2 ± 4.0	6.5 ± 3.6	
median (range)	11 (7-16)	10.5 (3-14)	8.5 (2-15)	6.5 (1-12)	
PDQ question 3**					
n	27	26	18	17	-
No n (%)	0 (0)	0 (0)	3 (17)	3 (18)	
Yes n (%)	27 (100)	26 (100)	15 (83)	14 (82)	
Curvature change***					
n	-	5	3	18	26
Worse n (%)		0 (0)	0 (0)	0 (0)	0 (0)
No change n (%)		0 (0)	0 (0)	2 (11)	2 (8)
Little decrease n (%)		3 (60)	1 (33)	6 (33)	10 (38)
Decrease n (%)		2 (40)	1 (33)	7 (39)	10 (38)
Significant decrease n (%)		0 (0)	1 (33)	3 (17)	4 (15)

* Differences between PDQ scores at baseline and PDQ scores at 6 weeks after the 1st, 2nd and 3rd cycles all statistically significant

** PDQ question 3: "Does your Peyronie's Disease make having vaginal intercourse difficult or impossible?"

*** Reported for patients who completed respectively 1, 2, 3 and 1-4 Collagenase Clostridium Histiolyticum injections



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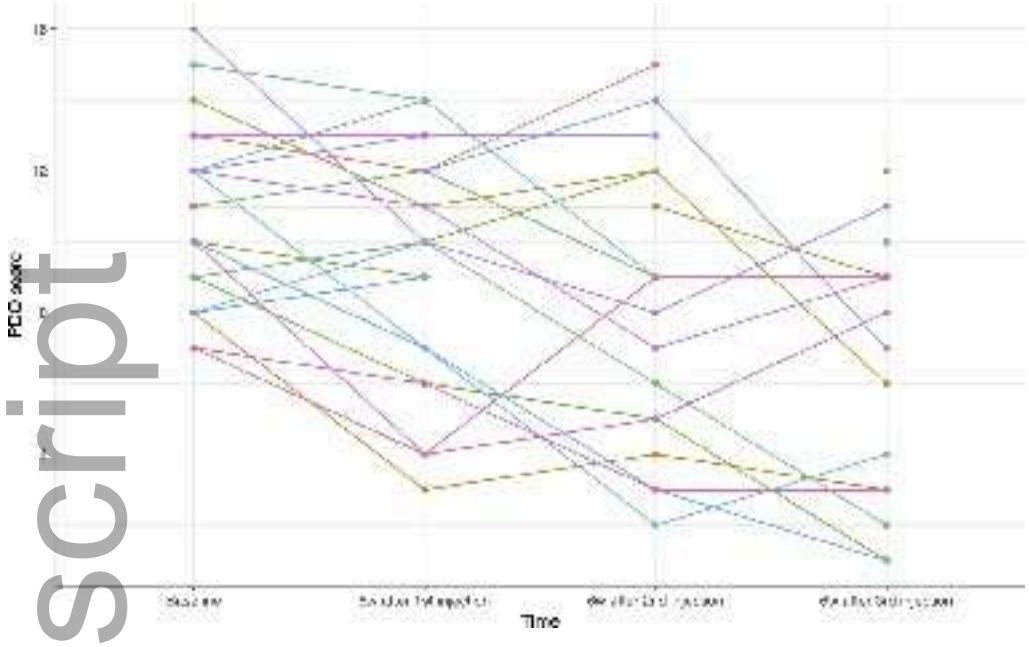

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