Plaque Calcification: An Important Predictor of Collagenase *Clostridium Histolyticum* Treatment Outcomes for Men With Peyronie's Disease

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OBJECTIVE To compare outcomes of men with or without calcified plaques undergoing collagenase *Clostridium histolyticum* (CCH) injections for Peyronie's disease (PD) and identify predictors of CCH success.

MATERIALS AND METHODS From March 2014 through January 2017, data were prospectively collected on 192 patients who underwent 1-4 cycles of CCH for the treatment of PD. Of these, 115 completed ≥2 CCH cycles and had data on curvature assessment. The primary outcome was the percentage of men with >20% improvement in composite curvature. Univariate analysis was performed to compare rate of success based on patient and disease characteristics, and multivariate logistic regression was used to identify predictors of successful treatment.

RESULTS Calcified plaques were identified in 34 of 115 (30%) patients. Patients with calcified plaque were younger, had longer duration of disease, and higher rates of significant erectile dysfunction. On multivariate logistic regression controlling for calcification and degrees composite curvature, non-calcified plaque (odds ratio 2.50; 95% confidence interval 1.06-6.00; P = .03) and curvature ≥60° (odds ratio 5.01; 95% confidence interval 1.34-21.62; P = .02) were found to be significant predictors of ≥20% improvement in composite curvature. When differentiated by calcification severity, those with no calcification achieved significant improvements in curvature (28.1° vs 10.3°, P = .04), compared to moderate (shadowing) or severe (>1 cm).

CONCLUSION Plaque calcification is associated with a significantly lower rate of success of CCH therapy for PD, while greater baseline curvature is associated with increased odds of successful curvature improvement. UROLOGY 00: 1–6, 2018. © 2018 Elsevier Inc.

Peyronie's disease (PD) is an acquired fibroconnective tissue disorder that affects between 0.4% and 13% of the male population.[1,2] Although the specific pathophysiology is unknown, it is believed to ultimately involve extravascular protein deposition and transformation of tunical collagen leading to plaque formation.[3] Such changes may be associated with pain, deformity, and erectile dysfunction and have a significant impact on quality of life.

Traditionally, surgical therapy has been considered the gold standard for curvature correction; however, in 2013, the Food and Drug Administration approved collagenase *Clostridium histolyticum* (CCH) for the treatment of PD. The efficacy and safety of CCH injections were demonstrated by two phase III multicenter randomized control trials.[4,5] The IMPRESS trials found significant reductions in penile curvature as well as symptom bother scores for patients receiving CCH injections vs placebo. Patients were excluded for curvatures <30° or >90°, ventral curvature direction, or plaque calcification that prevented injection.[4,5]

The efficacy of CCH was further supported by a postrelease study conducted by Ziegelmann et al. evaluating change in penile curvature and patient-perceived effect of CCH. Patients were found to have a 23° mean improvement in curvature, and 88% reported subjective improvements, with over 50% reporting restoration of penetration and negation of the need for surgery.[1]

Although CCH has been identified as an effective treatment for PD, there are minimal data regarding specific patient and disease characteristics that predict success. Plaque calcification has been identified as a potential poor predictor of response to nonsurgical therapy and may occur to some degree in up to one-third men with PD.[6] Patients with severe calcification may also exhibit an increased likelihood of progressing

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

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Submitted: March 21, 2018, accepted (with revisions): June 1, 2018

to surgical intervention.[7] Lipshultz et al. performed a *post-hoc* subgroup analysis of the IMPRESS trials to examine the efficacy of CCH based on clinical characteristics including degree of curvature, length of disease, calcification, and erectile dysfunction severity. Greater improvements in curvature were found among those with curvatures between 30° and 90°, disease duration greater than 2 years, no plaque calcification, and an international index of erectile function (IIEF) score $\geq$ 17.[8]

Although providing valuable insight into predicting CCH success, these studies were limited by the *post-hoc* analysis and the limitations of the IMPRESS trials. Specifically, the IMPRESS trials excluded men with calcification that potentially interfered with CCH injection. Therefore, the subgroup analysis described above was limited to patients with calcification that did not interfere with injection. Given that the IMPRESS trials were multicenter studies, it is unclear what level of calcification was used as an upper limit, and this likely differed between institutions. To date, no postrelease study has evaluated the effect of calcification on success of CCH. We therefore sought to prospectively evaluate a large cohort of men presenting with PD and electing to undergo treatment with CCH to assess patient and disease characteristics predictive of treatment success. We hypothesized plaque calcification would significantly reduce the success of CCH treatment.

MATERIALS AND METHODS

From March 2014 through January 2017, a prospective registry with detailed information on disease characteristics was maintained of all men undergoing CCH treatment for PD at our institution. Patients were considered for CCH treatment after undergoing physical exam and penile assessment in the flaccid and erect states, as well as penile duplex Doppler ultrasonography. As described previously, patients underwent intracavernosal injections with a standard formulation of 24 mg/mL papaverine, 1 mg/mL phentolamine, and 10 μg/mL alprostadil until maximum rigidity was achieved. Curvature assessment was performed with a goniometer in two planes. In cases of dorsolateral curvature, the larger measurement between the two planes was recorded as the primary curvature and the primary and secondary curvatures were combined and described as a composite curvature.[1]

All patients with an identifiable plaque on ultrasound and curvature between 30° and 90° were eligible for treatment, consistent with Food and Drug Administration-cleared indications. Patients with ventral curvatures were not included, as CCH is currently contraindicated in this population. However, those with plaque calcifications were not excluded, and all men were recommended CCH as a first-line therapy, regardless of calcification extent or severity. Patients were specifically counseled that patients with plaque calcification deemed to limit injection were not included in the original phase 3 clinical trials of CCH. Internal review board approval was obtained. Patients signed informed consent to permit release of their information for research.

The injection protocol consisted of two injections with each series at the point of maximum curvature, as measured from the glanular coronal margin with at least 6 weeks between series. The two injections were 1-3 days apart. After injection, the patients were instructed to perform modeling of the flaccid penis for 30 seconds with each void. Penile traction was encouraged for 1-3 hours daily during the treatment course.[1] Patients underwent curvature assessment at baseline, following 2 treatment cycles, and after 4 treatment cycles. These were performed by 1 of 4 providers. In addition, standardized patient questionnaires as well as outcome-based questions developed by a fellowship trained andrologist were completed by patients after each injection cycle regarding perceived improvements in curvature as well as sexual function, including ability to penetrate.

Patient demographics, clinical presentation, disease characteristics, treatment course, and treatment outcomes were evaluated. Plaque calcification, curve direction, degree of composite curvature, duration of disease, incidence of plaque indentation, or hourglass, IIEF score, peak systolic velocity, end diastolic velocity (EDV), and patient age were all assessed prior to treatment. With the exception of age, all variables were classified as categorical variables. Plaque calcification and degree of curvature categories were determined a priori. Plaque calcification was classified as none, mild (stippled calcification of any size without shadowing), moderate (identifiable shadowing $<$ 1 cm in size), or severe (identifiable shadowing $>$ 1 cm in size) (Fig. 1). Degree of curvature was categorized as 30°-60° and $>$60°. Mean peak systolic velocity and EDV were categorized into $<$30 cm/s vs $\geq$30 cm/s and $>$3 cm/s vs $\leq$3 cm/s respectively. Duration of disease was separated into less than 1 year, 1-2 years, and greater than 2 years. Lastly, IIEF score was classified as 1-10 (severe), 11-26 (moderate), 17-21 (mild to moderate), 22-25 (mild), and 26-30 (no dysfunction). The primary outcome was the percentage of men with $>$20% improvement in composite curvature based on curvature assessment. Secondary outcome was restoration in ability to penetrate assessed by post-treatment patient questionnaire.

Patient and disease characteristics were compared between patients with and without calcified plaques. *t* tests were used for continuous variables and chi-squared tests were used for categorical variables. Univariate analysis was performed to identify ultrasound findings and patient and disease characteristics predictive of successful outcomes. A multivariable logistic regression model for predictors of successful treatment ($\geq$20% improvement in curvature) was developed to include factors found to be significant on univariate analysis. A $P <$ .05 for 2-tailed tests was the threshold for statistical significance. A subset analysis was obtained evaluating the percentage change in composite curvature following treatment stratified by severity of plaque calcification. ANOVA was used to compare curvature improvement among patients with no calcification, mild calcification, and moderate or severe calcification. All statistical analysis was performed using JMP Pro software (SAS Institute Inc. Cary, NC).

RESULTS

From 2014-2017, 477 patients were presented to our institution for evaluation of PD. After initial evaluation and counseling, 192 patients completed at least 1 treatment of intralesional CCH injection therapy. Of these, 115 met inclusion criteria, completed $\geq$2 CCH cycles, and had data available on interval and/or final curvature assessments. These patients comprised the current cohort for evaluation.