

Collagenase clostridium hystolyticum in the management of Peyronie's disease

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Provenance: This is a Guest Editorial commissioned by Section Editor Yongde Xu, PhD (Department of Urology, First Hospital Affiliated to Chinese PLA General Hospital, Beijing, China).

Comment on: Yang KK, Bennett N. Peyronie's Disease and Injectable Collagenase Clostridium histolyticum: Safety, Efficacy, and Improvements in Subjective Symptoms. *Urology* 2016;94:143-7.

Submitted Dec 16, 2016. Accepted for publication Dec 19, 2016.

doi: 10.21037/tau.2017.01.15

View this article at: <http://dx.doi.org/10.21037/tau.2017.01.15>

Peyronie's disease (PD) is a connective tissue disorder characterized by inelastic fibrous plaques on the tunica albuginea of penis. Inelasticity induce penile deformity such as curvature, shortening, narrowing, hinging and also associated with penile pain and erectile dysfunction. The pathogenic mechanisms of the disorder are still poorly understood although physicians believed that the trauma to the tunica albuginea leads to excess inflammation in some men resulting in inflammatory mass formation in the early stage, then disruption of the normal cell architecture through deposition of collagen fibers and breaking down the elastic fibers create the "plaque".

PD has been known as incurable because of uncertain pathophysiology and no definite medical treatment. Various treatment modalities have been proposed including oral, topical (e.g., oral vitamin E, oral potassium para-aminobenzoate, tamoxifen, colchicine, carnitine, etc.) and injectable agents (e.g., intralesional or topical verapamil, steroid, interferon) (1). However, none of these agents are approved for treatment of PD and surgery still remains the mainstay treatment suggesting from the current ISSM guideline, but is only considered in patients who have reached the stable chronic phase of PD (at least 1 year from the time of onset and at least 6 months of no change in penile deformity) (2).

Since the first collagenase experimental study for PD by Gelbard *et al.*, in the 1982 (3), early clinical study indicated the potential for collagenase clostridium histolyticum

(CCH) to be used for the treatment of patients with PD (4-6). CCH is a mixture of AUX-I and AUX-II clostridial collagenase and it has been a treatment option for Dupuytren's contracture, pathology closely related to PD that causes a progressive deformity of the hand due to connective tissue contracture (7). Since the pathophysiology of Dupuytren's contracture and PD is similar, it is logical that utilization of CCH injection on fibrotic lesion in PD. CCH degrades the collagen type I and III selectively (the predominant collagen types found in PD plaques) resulting in the reduction of PD plaque but spared type IV, which is localized to vascular and nervous tissue (8). In the keeping with the safety and efficacy results from phase IIb and phase III trial (9,10), CCH (Xiaflex[®]) was approved by Food and Drug Administration (FDA) in December 2013 which is the only approved pharmacologic treatment option for treating PD. Based on two large multicenter phase III trials, investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies I and II (IMPRESS I and II), the recently published American Urology Association guidelines include CCH (in combination with modelling) as a treatment option for patients with PD and is indicated for the men with PD with stable disease, penile curvature >30° and <90°, and intact erectile function (10,11).

Postapproval studies of CCh have been anticipated after recent FDA authorization of its use for men with PD as definitive and durable nonsurgical interventions have been long desired. Recently, Yang and Bennett

conducted a postapproval early adopter series of CCH therapy for PD to provide independent validation of CCH use for PD patients (12). They concludes that the CCH injections are effective in the patient with PD, resulting in modest penile curvature reduction (15.4 degrees, 32.4%) and improvement of subjective bother symptoms (mean decrease 43.2%) and intercourse ability (29.1% improvement) which were consisted with outcomes from IMPRESS I and II trials (10,12). They also emphasized that compared to previous study, characteristics of the subject populations were diverse especially including active disease (defined as the onset of symptoms within 1 year of the first CCH injection or subjective reports of deformity changes before the first injection), hourglass deformity and ventral curvature. And they also identified meaningful reduction of penile curvature in these patients.

Expert opinion

In postapproval study of CCH, CCH use for PD yielded improvements in penile curvature, subjective intercourse, and bother symptoms. However there are some limitations to the study. First, the study includes a relatively small patient population and nonrandomized design with lack of a control group. The number of patients was too small to confirm the efficacy of CCH in active or acute phase of PD from only 12 patients and various progress in this phase is also confounding factor. Further study is needed to confirm clinical evidence for the use of CCH in active or acute phase of PD. Second, the objective efficacy end points only included the penile curvature. As the penile curvature measuring is also can be subjective, it would be better to measure changes in penile length, plaque size or plaque consistency for providing the efficacy of CCH. Finally, the CCH safety result from the study did not report characteristics of patients who suffered from significant bleeding events after CCH injection, especially about plaque location and previous CCH injection sites. As the dorsal tunica is much thicker, rupture rarely occurs in contrast to ventral tunica. Since the study included ventral plaque of PD, the occurrence of significant of hematoma and penile rupture following injection of CCH among these patients is important to identify the risk of ventral plaque injection.

The ideal characteristics of intralesional agent should degrade the abnormal fibrous deposit only and prohibit the tunical breakage from nonspecific degradation. And it also spares normal elastic fibers to preserve the tunical

elasticity with normal erection. Previously, accurate injection of topical agent into the plaque has been always debated. According to phase IIb and phase III trial, it is recommended that collagenase is directly injected into the primary plaque using 26 or 27 gauge at the point of maximal curvature (9,10). However, direct injection into the plaque is very difficult due to requiring high pressure and inelasticity of plaque. Inaccurate injection due to these difficulties may influence the efficacy. Also injection around the plaque may lead adverse bleeding event and pain from weakening of capillary wall and inflammatory reaction. Actually, most commonly reported treatment-related adverse events in previous trials were penile ecchymosis, penile pain and penile swelling. For the specific degradation of fibrous plaque, special injection technique should be developed and recommended. Besides of the injection technique, optimal dosing of CCH and schedule of CCH injection are very important for clinical application. Recent recommendations of CCH dosing and injection schedule are 0.58 mg of each injection with interval of approximately 24 to 72 hours between each injection (10). However, it is questioned whether different dose is suitable depends on patient's age, underlying disease, plaque size and disease duration. In addition, penile swelling, pain, ecchymosis often complain after the first injection are lead to postpone second injection because of residual tenderness and edema precluding accurate palpation of the plaque. After adjustment of ideal CCH dosing and injection schedule of each patient, CCH can be widely used in various countries including Asia.

The objectives of PD treatment are penile curvature reduction to restore ability of penetrative intercourse and pain relief. However, collagenase alone would not enough for treating PD. The best result of intralesional CCH can be obtained in combination with modelling to treat curvature in PD (9,10). As CCH with modelling does not treat pain or ED, another combination therapy is needed for managing these symptoms. The combination therapy, covering each different mechanism of drug action, was not only effective to ameliorate or prevent deterioration of the disease but also had beneficial effect even in compliance. Especially in patients whose curvature was less than 30 degrees showed better response to medical combination therapy (13). It suggests that early treatment may lead to better results in PD. Yang and Bennett also discussed about the phase of disease as determinants of different improvement of curvature (12). They questioned whether CCH can act as a disease modifier for PD in the active phase preventing exacerbation of symptoms and deformities

for PD states. This should be considered in the treatment of PD with CCH in those who suffered from mild penile curvature as early treatment.

Conclusions

According to several recent studies, intralesional CCH injection is a minimally invasive and can be safely and effectively used in a specific subgroup of patients with the aid of penile modelling. In the future, further study that analyzing of patients who are unlikely to respond will help establish of patients selection and indication of CCH in PD. We hope that a numerous postapproval study of CCH therapy in PD should conduct not only for long-term safety and efficacy but also establishment of the ideal treatment strategy including injection schedule, injection dose, injection technique and post procedure care.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Ahn ST, Moon DG. Collagenase clostridium histolyticum in the management of Peyronie's disease. *Transl Androl Urol* 2017;6(2):305-307. doi: 10.21037/tau.2017.01.15