REVIEW ARTICLE

Collagenase *Clostridium histolyticum* for the Treatment of Peyronie's Disease: The Development of This Novel Pharmacologic Approach

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ABSTRACT

Introduction. The conception of collagenase *Clostridium histolyticum* (CCH) as treatment for Peyronie's disease (PD) was a vital first step in providing a nonsurgical, minimally invasive FDA-approved treatment for men with PD.
Aim. To review the origins, clinical research history, and ultimately FDA approval of collagenase as PD treatment.
Methods. A PubMed search using (Peyronie's or Peyronie) AND collagenase, and limited to clinical research studies, returned nine papers that were examined in the current review.
Results. Collagenase as a PD treatment arose in response to a lack of effective nonsurgical treatments and the incomplete understanding of underlying PD etiology. Awareness of dense collagen in PD scarring and parallel initial exploration of collagenase to treat herniated lumbar discs coincided with and inspired laboratory-based investigation of collagenase effects on excised PD plaque tissue. The foundational conceptual work and the critical development of purified injectable collagenase allowed the pursuit of clinical studies. Progression of clinical studies into large-scale robust trials culminated in two important outcomes: development of the first validated, PD-specific measure of psychosexual function, the Peyronie's Disease Questionnaire, and the first FDA-approved treatment for PD.
Conclusions. Collagenase therapy began as an attempt to modify the structure of PD-related tunica albuginea scarring, despite the lack of a fundamental understanding of the scar's origin. If we wish to advance PD treatment beyond this first effective step, the future needs to bring us full circle to the starting point: We need a greater understanding of the control of collagen deposition and wound healing in men with PD. **Gelbard MK, Chagan L, and Tursi JP. Collagenase *Clostridium histolyticum* for the treatment of Peyronie's disease: The development of this novel pharmacologic approach. J Sex Med 2015;12:1481–1489.**

Key Words. Penile Induration; Peyronie's Disease; Microbial Collagenase

Introduction

Peyronie's disease (PD) is a localized fibrosing disorder involving primarily the tunica albuginea and, in some cases, linear fibers of the intracavernous struts and intercorporal septum. It is characterized by deposition of collagenous plaques, which may then result in penile curvature or other deformities [1,2]. While the specific etiological factors underlying PD remain under investigation, the presence of excessive collagen in PD appears to be a consequence of dysregulated collagen synthesis, a concept appreciated since the 1960s [3]. PD plaques have been shown to consist of disorganized and excessive collagen and fibrin and fragmented elastic fibers [1,4,5].

The concept of using collagenase as a rational treatment for the enzymatic modification of deforming penile scarring in PD arose from the juxtaposition of three fields of investigation: the discovery and characterization of collagenases produced by *Clostridium* species, early clinical investi-

gation of applications for collagenases, and the identification of excessive collagen in PD penile plaques. The hypothesis behind early collagenase research in PD was that enzymatic modification of the penile plaque should restore penile symmetry and function. Between enzymatic collagenolysis and restoration of sexual function lies a wide gap, and establishing causality between these two ideas necessarily involved a considerable amount of work. The result of these efforts has been collagenase *Clostridium histolyticum* (CCH), the first U.S. Food and Drug Administration (FDA)-approved treatment (2013) for men with PD with a palpable plaque and penile curvature deformity of at least 30° at the start of treatment. CCH injection into the primary penile PD plaque at the point of maximum penile curvature deformity, along with a penile modeling procedure, has been shown to improve penile curvature deformity and the PD bother score within the Peyronie's Disease Questionnaire (PDQ) [6]. The availability of CCH as a treatment for PD is a vital first step in providing men with PD an effective nonsurgical, minimally invasive treatment option.

Aim

The aim of the current review is to synthesize the conceptual and clinical research history of CCH for the treatment of PD. It is our hope that a better understanding of the origin of CCH treatment—from in vitro enzyme biochemistry through large-scale clinical trials—will provide the foundation for further advancement in the treatment of PD.

Methods

A PubMed search using the terms (Peyronie's or Peyronie) AND collagenase, and the limit of English, returned 32 articles. Following the exclusion of review articles and commentaries, nine clinical research papers examining in vitro and clinical studies of CCH in patients with PD were retained and evaluated in depth.

Results

Discovery of Collagenases

In 1952, Ines Mandl and colleagues were the first to isolate and characterize collagenases from *Clostridium histolyticum* cultures that were capable of enzymatic collagenolysis at physiologic temperature and pH [7]. Subsequent clinical development of treatments using collagenase have relied upon advances in purification of the enzyme and consequent improved levels of collagenase purity, and greater understanding of the spectrum of collagenases present in *Clostridium histolyticum* cultures [8–12]. Early work established three important outcomes. First, the presence of a potent collagenase in culture media from *Clostridium histolyticum* was demonstrated. Second, the process for the separation of collagenase from nonspecific protease activity was developed. Third, selective collagenase activity was shown against native collagen but not casein, hemoglobin, albumin, or fibrin [8,9]. In later work, different molecular forms of collagenases capable of degrading interstitial collagens were isolated from crude collagenase product, and the identification/classification of these forms within class I or II collagenases was shown [10]. The two classes of collagenases from *Clostridium histolyticum* were revealed to have complementary effects through different initial cleavage of sites of the collagen triple helix, either close to the C-terminus (class I) or at the interior of the triple helix (class II). Synergy of the activity of the two classes of collagenase in degradation of collagen was later demonstrated [11,12].

Early Development of Collagenase Clinical Applications

The First Interdisciplinary Symposium on Collagenase was convened in 1970 to review research on CCH and its earliest clinical applications [13]. Among a broad range of tissue culture, in vitro, and animal model studies, researchers presented their initial work using collagenase for intervertebral discolysis, debridement of burns and dermal ulcers, and as an adjunct to cryoprostatectomy [13–17]. In particular, the application of collagenase injection to the treatment of lumbar intervertebral herniated discs was influential in the conceptual origin of collagenase as a treatment for PD. In cases of disc-related sciatica, the herniated nucleus pulposus compressing the nerve root was known to have a high soluble collagen content. The ability of collagenase to dissolve the collagen, liquefying the protruding nucleus and thereby relieving pressure on the nerve, was examined in a series of in vitro and animal model studies, as reviewed by Bernard Sussman and Mann [14]. Prior to collagenase, the enzyme chymopapain had been used to target the mucopolysaccharide component of the herniated nucleus. Unfortunately, it was associated with adverse events related to aller-