Advances in the Management of Dupuytren Disease
Collagenase

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KEYWORDS

• Dupuytren disease • Collagenase • Myofibroblasts • Connective tissue disorder

KEY POINTS

- Dupuytren disease is a benign, generally painless connective tissue disorder affecting the palmar fascia that leads to progressive hand contractures.
- Mediated by myofibroblasts, the disease most commonly begins as a nodule in the palm or finger.
- If the disease progresses, pathologic cords form leading to progressive flexion deformity of the involved fingers, commonly of the metacarpal-phalangeal and proximal interphalangeal joints, but also of the distal interphalangeal joint, and the first web space.

INTRODUCTION

Dupuytren disease (DD) is a benign, generally painless connective tissue disorder affecting the palmar fascia that leads to progressive hand contractures. Mediated by myofibroblasts, the disease most commonly begins as a nodule in the palm or finger. If the disease progresses, pathologic cords form leading to progressive flexion deformity of the involved fingers, commonly of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, but also of the distal interphalangeal joint, and the first web space. The palmar skin overlying the cords may become excessively calloused and contracted and involved joints may develop periarticular fibrosis. This is particularly true of the PIP joints. Although there is as yet no cure, the sequellae of this affliction can be corrected.

TREATMENT OF DD AND THE OUTCOMES OF TREATMENT

Treatment for DD was first described by Henry Cline[1] in the late seventeenth century and involved sectioning the pathologic cords, later known as fasciotomy or aponeurotomy. Since then surgical intervention traditionally has been the most effective and widely accepted treatment for progressive contracture. Today's surgical options include limited percutaneous needle aponeurectomy, open versus percutaneous fasciotomy, and the more commonly performed open fasciectomy. Until recently, nonsurgical interventions, such as injectable corticosteroids or verapamil, have proved to be largely ineffective for the treatment of contractures and rejected clinically. Collagenase *Clostridium histolyticum* (CCH) was introduced to the literature slightly more than

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15 years ago[2] as a potential minimally invasive, nonsurgical option to treat Dupuytren contractures. This has ultimately led to completion of phase 3 clinical trials and its recent US Food and Drug Administration (FDA) approval for clinical use under the marketed name Xiaflex. In Europe, the drug is marketed as Xiapex. The remainder of this article focuses on the role of collagen in DD and the development of a collagen-specific enzymatic treatment for DD contractures and early post-FDA product release results.

THE ROLE OF COLLAGEN IN DD

Luck[3] described the pathogenesis of Dupuytren contracture in pathologic terms consisting of proliferative, involutional, and residual phases. The proliferative phase is characterized by nodule formation within the palmar fascia. Fibroblasts differentiate into myofibroblasts and comprise most of the nodular architecture. Myofibroblasts are fibroblastic in origin; however, they contain actin microfilaments that communicate with the extracellular matrix fibronectin, thereby allowing transmission of intracellular contractile forces to the extracellular tissues.

Marked nodular thickening and early joint contracture characterize the involutional phase. A preponderance of type III collagen is synthesized and the myofibroblasts reorient along the lines of tension within the palm. Type III collagen is a hallmark of the disease because it is not typically observed within the mature palmar fascia of patients unaffected by DD.[4,5]

Myofibroblasts have largely disappeared by the residual phase, resulting in a relatively hypocellular amalgam of type I and type III collagen.[3,6,7] This process results in the conversion of normal palmar and digital fascial structures into fibrotic Dupuytren cords, which are clinically manifested as contractures of the joints of the hand. This evolution in the understanding of the molecular pathogenesis of DD has provided a host of potential nonsurgical therapeutic clinical targets for treatment.

ENZYMATIC FASCIOTOMY

The concept of targeting abnormal collagen was first reported by Bassot[8] in 1965, with his technique of "exerese pharmodynamique," which used a mixture of trypsine, alphachymotrypsin, hyaluronidase, thiomucase, and lignocaine and degraded the proteinaceous component of the pathologic cords, allowing for rupture. Bassot's[9] results in 1969 showed an impressive correction of severe contractures in 34 patients. In 1971, Heuston[10] reported his experience with trypsin, hyaluronidase, and marcaine, achieving favorable initial results. McCarthy[11] reported his experience with enzymatic fasciotomy in 14 patients, noting recurrence of initial contracture in 75% of patients at an average of 2- to 3-year follow-up. He expressed concern regarding the possibility of tendon rupture and neurovascular injury as a consequence of nonspecific enzymatic degradation of the palmar tissues, although no frank ruptures or neurologic sequelae were reported.

COLLAGENASE *CLOSTRIDIUM HISTOLYTICUM*

CCH, long available and frequently used in laboratory research, emerged as a potential therapeutic option for the treatment of DD in 1996, offering the potential advantage of target specificity. CCH, first discovered in the culture media of *C histolyticum* and reported by Maclennon and coworkers in 1953,[12] is one of several matrix metalloproteinase enzymes responsible for the degradation of extracellular matrix components. CCH, structurally and functionally related to endogenous human collagenase enzymes, is encoded in two distinct genes: *ColG* and *ColH*. Seven distinct enzyme isoforms have been recognized belonging to two separate classes, designated class I (*ColG*) and class II (*ColH*).

Pharmacokinetics

Commercially available CCH consists of a defined mixture of a class I collagenase (termed Aux I by the manufacturer) and class II collagenase (termed Aux II) isoforms that work synergistically on all types of collagen, with the exception of type IV collagen (**Fig. 1**). Type IV collagen is the primary collagen component of basement membranes of neurovascular structures and ex vivo studies have demonstrated preservation of arterioles, nerves, and epithelia after local injection of collagenase.[2,13,14]

There is limited systemic absorption after local injection suggesting the ability of the renal system to concentrate and excrete collagenase. The remainder of the injected collagenase is thought to bind to endogenous serum proteins that are subsequently eliminated by the liver. In vitro studies and in vivo clinical experience suggests that most CCH activity is confined to the region of local tissue infiltration and that its catalytic activity against collagen persists for less than 24 hours.[2]

CLINICAL STUDIES IN DD

Topical application of collagenase has been performed for more than four decades and its use in