Collagenase clostridium histolyticum: a novel nonoperative treatment for Dupuytren's disease

Collagenase clostridium histolyticum has demonstrated safety and efficacy in the treatment of metacarpophalangeal and proximal interphalangeal joint contractures in Dupuytren's disease as a 0.58-mg dose delivered via direct injection into the Dupuytren's cord. Extension is achieved via manual manipulation 24 h following injection. Commercially available collagenase clostridium histolyticum is a combination of class I and class II collagenases that act in concert to degrade the type I and type III collagen content of pathologic Dupuytren's cords and is available to practitioners who have completed focused training in injection technique. This article reviews collagenase clostridium histolyticum pharmacodynamics as well as the basic science and clinical studies resulting in US FDA and EMA approval for the treatment of Dupuytren's disease. Clinical indications, technique and an analysis of future indications are reviewed.

KEYWORDS: collagenase ■ Dupuytren's disease ■ nonoperative ■ Xiaflex® ■ Xiapex®

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Dupuytren's disease is a progressive disease of the palmar and digital fascial structures of the hand characterized by abnormal collagen deposition, nodular thickening of the palmar aponeurosis and subsequent joint contracture. Contracture occurs primarily at the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joint levels (Figure 1). Although pathologically benign, Dupuytren's contracture results in significant functional debility of the hand with a strong propensity toward disease progression and recurrence.

The incidence of Dupuytren's disease varies from 2 to 42%, depending on the population under investigation, with a higher incidence found among populations of northern European descent [1]. Inheritance is generally considered to be autosomal dominant with variable penetrance; however, complex inheritance patterns have been suggested. Disease expression typically becomes apparent with advancing age, with men typically demonstrating initial signs of the disease in the 5th decade of life, and women in the 6th. A notable exception to this trend is in patients with a Dupuytren's diathesis characterized by early onset, typically severe and often bilateral disease.

Although Dupuytren's disease has been formally recognized and clinically treated for over two centuries, it has only been over the past 30 years that surgeons and scientists have begun to unravel the cellular mechanisms that contribute to the development of Dupuytren's disease. Histopathologic studies have revealed nodular condensations of fibroblasts surrounded by dense collagen within the palmar and digital fascia, and molecular analysis reveals a preponderance of type III collagen within the Dupuytren's cords. Type III collagen is a hallmark of the disease as it is not typically observed within the mature palmar fascia of patients unaffected by Dupuytren's disease [2,3].

Luck described the pathogenesis of Dupuytren's contracture in pathologic terms consisting of proliferative, involutional and residual phases [4]. This description has provided a framework within which molecular advances may be analyzed as well as a foundation for clinicians' understanding of disease progression. The proliferative phase is characterized by nodule formation within the palmar fascia and biochemically by increased fibrinolytic activity. At this stage, fibroblasts differentiate into myofibroblasts and comprise the majority of nodular architecture. Myofibroblasts are fibroblastic in origin; however, they contain an actin microfilamentous structure analogous to that found in smooth muscle cells. These actin microfilaments are arranged in bundles oriented along the long axis of the cell and communicate with the extracellular matrix fibronectin, thereby allowing transmission of intracellular contractile forces to the extracellular tissues. Marked nodular thickening and signs of early joint contracture characterize the involutional phase. Throughout the involutional phase, type III collagen is synthesized and the myofibroblasts reorient along the lines of tension within the palm. Type III collagen deposition continues and is gradually replaced with type I collagen throughout the residual phase.

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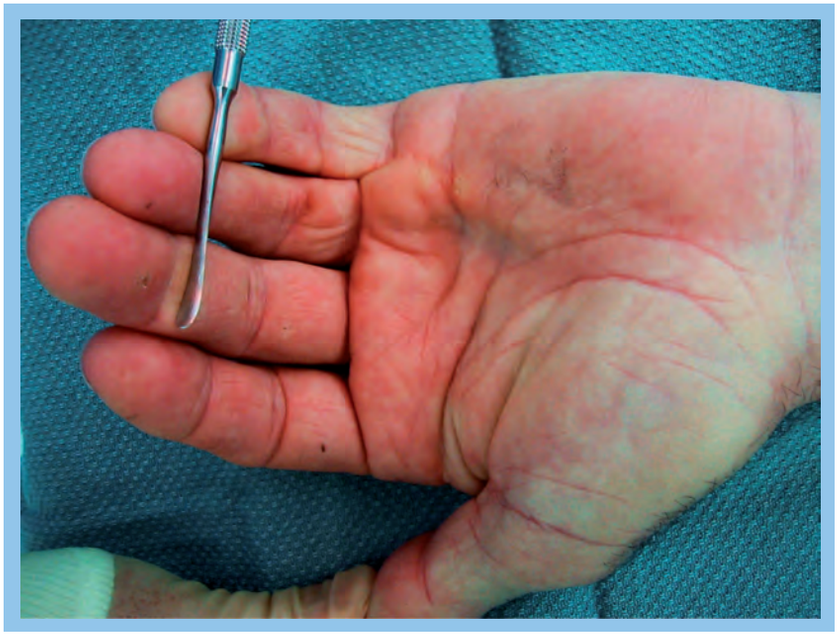

Figure 1. Dupuytren's contracture.

Myofibroblasts have largely disappeared by the residual phase, resulting in a relatively hypocellular amalgam of type I and type III collagen [4–6]. This process results in the conversion of normal palmar and digital fascial structures into fibrotic Dupuytren's cords, which are clinically manifest as contractures of the joints of the hand.

This evolution in the understanding of the molecular pathogenesis of Dupuytren's disease has provided a host of potential therapeutic clinical targets for treatment. Over the past four decades numerous nonoperative interventions have been introduced including extension splinting, ultrasound therapy, external beam radiation therapy, as well as treatment with dimethyl sulfoxide, vitamin E, methylhydrazine, allopurinol, colchicine, IFN-γ and both injectable and systemic corticosteroids [7–18]. This multitude of nonoperative interventional procedures underscores both physician and patient desire to develop a viable nonsurgical option for the treatment of Dupuytren's disease. Despite persistent efforts, these interventions have met with little to no clinical success, and surgical intervention in the form of fasciectomy has remained the mainstay of treatment in Dupuytren's disease. A notable exception to these clinical failures has been the development of the technique of enzymatic fasciectomy.

The concept of targeting abnormal collagen deposition with an enzymatic fasciotomy was first reported by Bassot in 1965 with his technique of 'exerese pharmodynamique' [19]. This therapy utilized a mixture of trypsine, alphachymotrypsin, hyaluronidase, thiomucase and lignocaine, which degraded the proteinaceous component of the pathologic cords, allowing for rupture. Bassot's results in 1969 showed an impressive correction of severe contractures in 34 patients [20]. In 1971, Heuston reported his experience with a simplified formula consisting of trypsin, hyaluronidase and marcaine, achieving favorable initial results [21]. McCarthy reported his experience with enzymatic fasciotomy in 14 patients, noting recurrence of initial contracture in 75% of patients at an average of 2–3-year follow-up. He concluded that there was a similar rate of recurrence with both enzymatic fasciotomy and surgical fasciectomy; however, he expressed concern regarding the possibility of tendon rupture and neurovascular injury in the setting of a nonspecific enzymatic degradation of the palmar tissues [22]. No frank ruptures or neurologic sequelae were reported in his study; however, the technique of enzymatic fasciotomy fell into disfavor given these concerns regarding lack of target specificity.

Clostridial collagenase, long available and frequently used in laboratory research, emerged as a potential therapeutic option for the treatment of Dupuytren's disease in 1996, offering the potential advantage of target specificity. Clostridial collagenase has subsequently been evaluated both *in vitro* and *in vivo* and has recently been approved by the US FDA and the EMA for the treatment of Dupuytren's contracture. This article will review the biomolecular properties of collagenase clostridium histolyticum as well as the existing clinical evidence regarding its efficacy and safety in the treatment of Dupuytren's disease.

Collagenase clostridium histolyticum

Collagenase clostridium histolyticum was first discovered in the culture media of *Clostridium histolyticum* and was reported by Maclennon in the medical literature in 1953 [23]. Since that time, collagenase clostridium histolyticum has been further characterized and widely employed as a workhorse in the basic science laboratory and as a potential therapeutic enzyme in a host of disease processes.

Clostridial collagenase belongs to the overarching category of matrix metalloproteinase enzymes whose principal role remains degradation of extracellular matrix components. Clostridial collagenase is structurally and functionally related to endogenous human collagenase enzymes that allow for turnover and remodeling of nearly all collagen-containing tissues throughout the body.

The structure of collagenase clostridium histolyticum is encoded in two distinct genes: *ColG* and *ColH*. *ColG* and *ColH* gene transcription and translation result in the synthesis of seven distinct enzyme isoforms that differ with respect to the location of their carboxy terminus. *ColG* encodes a 116-kDa, 1008-amino acid protein, while *ColH* encodes a similar 116-kDa, 981-amino acid protein sequence. Both genes are known to encode a variety of gelatinase enzymes that are the result of proteolytic cleavage of the initial gene product [24]. The resultant collagenase enzymes are similar in structure and function. Both enzymes contain two essential domains: a collagen-binding domain which requires calcium for the maintenance of appropriate structure and a catalytic domain which utilizes zinc as an essential cofactor for activation [25]. These two collagenase isoforms belong to two separate classes of collagenase enzmes, designated class I (ColG) and class II (ColH). These classes appear to have different evolutionary origins and differ primarily in substrate specificity. Class II collagenases generally exhibit less substrate specificity, target internal peptide sequences for cleavage and demonstrate higher affinity for small peptides and denatured collagen, whereas class I collagenases are highly specific with respect to their proteolytic targets with high affinity for the intact, triple-helical collagen, acting primarily at the N- and C-terminal domains. The net effect is that these two collagenase isoforms are complimentary and work synergistically to degrade a variety of collagen types [26–29].

Commercially available collagenase clostrudium histolyticum (marketed as Xiaflex® [Auxilium Pharmaceuticals, Inc.] in the USA and Xiapex® [Pfizer] in Europe) consists of a mixture of a class I collagenase (Aux I) and class II collagenase (Aux II) isoforms in a defined mass ratio. These isoforms function in their constitutive or native forms and do not require proteolytic cleavage for activation. These isoforms work synergistically with a broad catalytic effect on all types of collagen, with the exception of type IV collagen. Sparing of type IV collagen from the degradative profile may have clinical relevance as type IV collagen is the primary collagen component in the basement membranes of neurovascular structures and *ex vivo* studies have demonstrated preservation of arterioles, nerves and epithelia following local injection of collagenase **(Box 1)** [30–32].

Collagenase clostridium histolyticum is directly injected into Dupuytren's cords, exerting its lytic effects within the local tissue. Clinical absorption studies have demonstrated limited systemic absorption following local injection and manipulation in the treatment of Dupuytren's disease. Urine and serum samples were obtained as a component of the initial Phase II clinical studies. Four patients receiving a local injection of 10,000 units of collagenase clostridium histolyticum excreted 7–28% of the injected dose, with excretion noted between 30 and 60 min after injection [33]. No detectable serum levels were noted, suggesting the ability of the renal system to concentrate and excrete collagenase following local injection. The remainder of the injected collagenase is thought to bind to endogenous serum proteins forming enzyme-inhibitor complexes that are subsequently eliminated by the liver. Collagenase is not a substrate for drug-metabolizing pathways and presents no potential for interaction with the cytochrome P450 metabolic pathway. Formal metabolic and volume of distribution studies have not been conducted; however, *in vitro* studies and *in vivo* clinical experience suggests that the majority of collagenase clostridium histolyticum's activity is confined to the region of local tissue infiltration and that its catalytic activity against collagen persists for less than 24 h [30].

Clinical efficacy

Ex vivo & animal studies

Initial clinical studies on collagenase clostridium histolyticum were performed in the context of Peyronie's disease. Peyronie's disease is a benign fibromatosis involving the tunica albuginea of the penis, clinically resulting in deviation during erection. The plaque in Peyronie's disease is biochemically similar to Dupuytren's cords and the two diseases are often comorbid. In 1982, Gelbard and colleagues studied collagenase efficacy *in vitro* on specimens obtained from patients with Peyronie's disease. Plaques from patients with Peyronie's disease as well as normal tunica albuginea were injected with 400 units of clostridial collagenase and analyzed 24 h postinjection. Weight analysis supported degradation of the collagen component of these specimens with loss of 80–99% of their pre-injection weight. Histologic analysis demonstrated the degradative effects to

Box 1. Characteristics of collagenase clostridium histolyticum.

- Trade name: Xiaflex® or Xiapex®
- Composition: class I (Aux I) and class II (Aux II) collagenase
- Clinical target: all collagen isoforms (except type IV)
- Mechanism of action: catalytic cleavage of triple-helical collagen structure
- Method of administration: focal injection (0.58 mg)

be confined to the region of injection with no evident degradation of elastic tissue and/or vascular structures [32].

Badalamente and colleagues examined the effects of collagenase in a rat tail tendon model. Doses of 150 and 300 units were injected to determine the degree of local extravasation. The enzymatic effects of collagenase were confined to 0.5 cm proximal and distal to the site of injection, supporting the conclusion that the catalytic effects are focal and confined to the site of injection [33].

Starkweather and colleagues conducted the first reported *in vitro* experiments utilizing Dupuytren's cords obtained from patients undergoing surgical fasciectomy [30]. These specimens were injected with varying doses of collagenase clostridium histolyticum and tested to determine the tensile modulus (uniaxial stress/uniaxial strain) or resistance to rupture. The dose–response component analysis revealed a direct correlation between increasing collagenase dose and weakness of the Dupuytren's cord (150, 300 and 600 units). A dose of 300 units was determined to be the minimum effective dose needed to cause cord rupture with a physiologic extension force. Histologic analysis demonstrated increased collagen lysis in direct proportion to increased doses of injectable collagenase. Starkweather's key finding, that 3600 units of collagenase resulted in a 93% decrease in the tensile modulus of a Dupuytren's cord and led to complete disruption of the cord in three out of ten specimens, has provided the basis for subsequent clinical investigation and dosing in Dupuytren's disease [30].

Human studies

Topical application of collagenase has been employed clinically for over four decades and its use in the treatment of chronic ulcers and burns is well tolerated and widely accepted [34]. The use of injectable collagenase clostridium histolyticum was first described for the treatment of Peyronie's disease. Gelbard and colleagues conducted a series of clinical trials demonstrating that collagenase may be injected into penile plaques in a safe and efficacious manner [32,35,36]. Hamilton examined the systemic immune response to injectable collagenase, drawing serum samples from 44 patients undergoing collagenase injection for the treatment of Peyronie's disease. One patient developed IgE antibodies to collagenase, while all patients exhibited a two- to ten-fold increase in anticollagenase IgG; however, no systemic sequelae were noted. The authors concluded that the development of a significant systemic immune response, including a type IV hypersensitivity reaction, would be unlikely [37].

In total, 13 clinical studies have been conducted on injectable collagenase clostridium histolyticum: one Phase I, three Phase II and nine Phase III, culminating in FDA and EMA approval in February 2010. Although much of these data remain unpublished and many of the studies have been financially supported by the drug's manufacturer, a viable body of literature exists regarding the safety, efficacy and initial long-term outcomes for the treatment of Dupuytren's disease with injectable collagenase clostridium histolyticum.

The results of Phase I and Phase II clinical trials are well summarized in a set of publications from Badalamente and Hurst [38,39]. These initial studies focused on establishing a safety profile, appropriate dosing and refining injection technique. These early studies were conducted with commercially available clostridial collagenases with variable ratios and mixtures of collagenase isozymes. The initial study was conducted as an open-label trial in 35 patients with Dupuytren's disease. Six patients were treated with a dose-escalation protocol consisting of sequential 300-, 600-, 1200-, 2400-, 4800- and 9600-unit doses of clostridial collagenase injected into associated Dupuytren's cord. These doses were documented to result in no clinical response. The remaining 29 patients received an injection dose of 10,000 units of clostridial collagenase. Of the patients treated for MCP joint contracture, 28 out of 34 joints (82%) corrected to normal extension within 2 weeks of injection. Of the patients treated for PIP joint contracture, four out of nine joints (44%) corrected to normal extension within 2 weeks of injection. Within this patient population there were two treatment failures. The authors concluded that clostridial collagenase "appears to have merit as a nonsurgical treatment of this disorder" [38].

The open-label study was followed by a multicenter, double-blind, placebo-controlled Phase IIb trial enrolling 80 patients with Dupuytren's disease. This study was specifically designed to examine dose response, pharmacokinetics and clinical outcomes. A total of 80 patients were enrolled and randomized to receive either placebo or a 2500-, 5000- or 10,000-unit dose of clostridial collagenase. Subgroup analysis revealed that 18 out of 23 patients who received 10,000 units of collagenase achieved normal extension at 1 month compared with ten out of

22 who received 5000 units and nine out of 18 who received 2500 units. No response to placebo injection was seen in any patient. Hazard function analysis demonstrated a 90% success rate in patients with MCP contractures and 70% in patients with PIP contractures.

The results of the Phase II clinical studies laid the groundwork for subsequent Phase III clinical investigation. Initial Phase III clinical trial results were published in 2007 by Badalamente and Hurst [39]. This study was designed as a double-blind, placebo-controlled trial with an open-label extension. A total of 35 patients were enrolled and 33 patients completed the study. In total, 23 patients underwent injection with 10,000 units of collagenase clostridium histolyticum while 12 patients received placebo injections. A maximum of three injections, of 10,000 units each, for a single joint contracture were performed at 4–6-week intervals. Patients who achieved complete correction after a single injection at the primary joint were eligible for randomization and injection at a second site of contracture. Patients who received placebo injections or who failed to have complete correction during the double-blind portion of the study were eligible for the open-label extension. Clinical success was defined as extension to within 0–5° of full extension.

Of the 23 patients randomized to receive collagenase clostridium histolyticum injection, 16 (70%) achieved clinical success with a single injection, two (9%) achieved clinical success with two injections and three (13%) achieved clinical success with three injections. In total, 21 out of 23 patients achieved correction of contracture to within 0–5° of full extension with a mean of 1.4 injections. Correction was achieved in 12 out of 14 (86%) primary MCP joints and in nine out of nine (100%) PIP joints (Table 1).

Of the 33 patients who completed the double-blind phase, 19 entered the open-label extension. In total, 35 joints were treated (16 MCP, 19 PIP) and 17 out of 19 (89.5%) achieved clinical success in at least one treated contracture. Correction was achieved in 14 out of 16 (88%) patients with MCP joint contractures and 13 out of 19 (68%) patients with PIP joint contractures. Five patients were noted to have recurrence after 24-month follow-up.

No major adverse events were reported; however, a number of minor, primarily injection-specific adverse events were noted. These minor adverse events included injection site pain in 100% of patients receiving collagenase and 50% of patients receiving placebo injection. Edema was noted in 100% of patients receiving collagenase injection and 8% of patients receiving placebo injection. Additional adverse events in patients receiving collagenase injections included ecchymosis (43%), skin laceration at cord rupture (13%) and lymphadenopathy (39%) [39].

This initial Phase III clinical trial was followed by the largest Phase III trial, whose results were reported in the *New England Journal of Medicine* in 2009 [40]. The Collagenase Option for Reduction of Dupuytren's (CORD) I study was designed as a 90-day, randomized, double-blind, placebo-controlled study with an open-label extension. This study employed the fixed mass ratio Xiaflex preparation of collagenase clostridium histolyticum. The study enrolled 308 patients with Dupuytren's disease with MCP and/or PIP contracture of 20° or more from 16 participating centers. The primary end point for clinical success was defined as a reduction in a primary joint contracture to 0–5° of full extension within 30 days of the last injection and injections were limited to three or fewer at a single level of contracture. A total of 741 injections were performed, 444 of which were with collagenase clostridium histolyticum while 297 were placebo injections. The primary end point was met in 102 out of 133 (76.7%) patients with MCP joint contractures and in 28 out of 70 (40%) with PIP joint contractures. Overall, the primary end point of reduction of primary joint contracture to within 0–5° of full extension was met in 130 out of 203 (64%) patients. The average reduction in joint contracture was 50.2°. The percent change in contracture from baseline was 87.1% in patients with MCP joint contracture and 64.5% in patients with PIP joint contracture. Overall change in contracture from baseline was 79.3% (Table 2). Notably, the severity of pre-injection contracture negatively predicted the response to treatment. Patients presenting with more severe contractures were significantly less likely to attain the primary end point. Specifically, 88.9% of collagenase-injected MCP joints with a baseline contracture of 50° or less met the primary end point, as compared with 57.7% of such joints with a baseline contracture of more than 50°. In total, 80.9% of the collagenase-injected PIP joints with a baseline contracture of 40° or less met the primary end point, as compared with 22.4% of such joints with a baseline contracture of less than 40°.

Adverse events were documented in 197 out of 204 (96.6%) of patients receiving collagenase injection and in 22 out of 104 (21.2%) patients receiving placebo injection. The majority of

Table 1. Summary of Phase II clinical trials.

Clinical study (year)	Study design	Patients enrolled (n)	MCP contracture (n)	PIP contracture (n)	Ref.
Badalamente and Hurst (2000)	Open label	35	28/34 (82%)†	4/9 (44%)†	[38]
Badalamente and Hurst (2007)	Double blind, placebo controlled	80	12/14 (86%)‡	9/9 (100%)‡	[39]

†Clinical success defined as correction to normal extension within 2 weeks of injection, single injection.
‡Clinical success defined as correction to normal extension within 1 month of final injection, patient received up to three injections.
MCP: Metacarpophalangeal; PIP: Proximal interphalangeal.

adverse events were consistent with local reaction to injection including peripheral edema (72.5%), contusion (51%), injection site hemorrhage (37.3%), injection site pain (32.4%) and skin laceration with manipulation (10.8%). Three out of 204 patients experienced major adverse events. One patient developed complex regional pain syndrome following injection and two patients experienced flexor tendon ruptures following collagenase injection. Surveillance for systemic complications did not reveal any significant adverse events. Serum assay for antibodies to type I (Aux I) and type II (Aux II) were positive in 85.8% of patients after a single injection, with 100% of patients exhibiting positive antibody titers after three injections. Despite this immune recognition, no hypersensitivity reactions were reported [40].

Data published from the CORD II study largely reiterate the efficacy and safety of collagenase clostridium histolyticum injection in the treatment of Dupuytren's disease [41]. The study enrolled 66 patients with Dupuytren's disease with MCP and/or PIP contracture of 20° or more from five participating centers. Analagous to the CORD I study, clinical success was defined as reduction of primary joint contracture to 0–5° of full extension within 30 days of the last injection and injections were limited to three or fewer at a single level of contracture. The primary end point was met in 13 out of 20 (65.0%) patients with MCP joint contractures and in seven out of 25 (28.0%) with PIP joint contractures. Overall, the primary end point of reduction of primary joint contracture to within 0–5° of full extension was met in 20 out of 45 (44.4%) patients. Analagous to the CORD I study, joints with a low baseline contracture severity responded better to injection than those with a high baseline contracture severity. Although direct comparison of primary end points suggests that patients enrolled in CORD I demonstrated greater efficacy in attaining the primary end point, examination of the number of patients achieving reduction in contracture to 15° or less (74% in CORD I, 67% in CORD II) suggests that these studies may be more comparable than the primary end point alone might suggest. Minor adverse events including edema, contusion and injection site pain were common. A small finger flexor pulley rupture was reported as the only major adverse event. No recurrences were noted within the 1-year follow-up period [41].

Data regarding the long-term efficacy and durability of collagenase clostridium histolyticum injection are scarce. Currently, only a single study has ventured to quantify the long-term efficacy of collagenase injection. This study followed a subset of the patients enrolled in the Phase II dose–response clinical trial at 8 years following initial treatment. Recurrence was stringently defined as any increase in the degree of contracture compared with maximal extension achieved following injection. Six patients were treated for MCP contracture

Table 2. Summary of Phase III clinical trials.

Clincial study (year)	Study design	Patients enrolled (n)	MCP contracture	Mean change in MCP range of motion	PIP contracture (n)	Mean change in PIP range of motion	Ref.
Hurst *et al.* (2009); CORD I	Multicenter, double blind, placebo controlled	308	102/133 (76.7%)†	40.6°	28/70 (40.0%)†	29.0°	[40]
Gilpin *et al.* (2010); CORD II	Multicenter, double blind, placebo controlled	66	13/20 (65.0%)†	42.0°	7/25 (28.0%)†	32.2°	[41]

†Clinical success defined as correction of contracture to within 0–5° of full extension within 30 days of last injection, patient received up to three injections.
CORD: Collagenase Option for Reduction of Dupuytren's; MCP: Metacarpophalangeal; PIP: Proximal interphalangeal.

with an average pre-injection contracture of 57°. Recurrence was noted in four out of six patients (66%) at 8-year follow-up with an average contracture of 22°. Two patients were treated for PIP contracture with an average pre-injection contracture of 45°. Recurrence was noted in two out of two patients (100%) at 8-year follow-up with an average contracture of 60°. No patients underwent further intervention on the treated finger and four out of the eight patients met operative indications (MCP contracture >30°; PIP contrature >0°). Patient satisfaction with injection was high, with seven out of eight patients stating that they would pursue collagenase injection for the treatment of recurrent or progressive disease [42].

Safety

Periprocedural complications

Although adverse events were noted in nearly all patients receiving collagenase injection, the incidence of major adverse outcomes was low. The majority of these complications may be categorized as self-limited, periprocedural complications including peripheral edema, ecchymosis, injection site pain, skin tears with manipulation and adenopathy. All results from both published and unpublished Phase I, II and III trials were combined in the FDA report. In total, 2630 collagenase injections were performed on 1780 cords in 1082 patients (Table 3). No clinically significant difference in the incidence of adverse outcomes was noted among subgroups (age, weight, gender, diabetes mellitus, location of injection) or inpatients receiving multiple sequential objections [101].

Major treatment-related events included three patients with flexor tendon ruptures (0.27%) and a single patient who developed complex region pain syndrome following injection (0.09%). The three flexor tendon ruptures were attributed to collagenase clostridium histolyticum injection into the flexor tendon sheath resulting in degradation of the collagen component of the tendon substance. These patients ultimately went on to require staged flexor tendon reconstruction. Staged flexor tendon repair within zone II of the flexor tendon sheath is a significant and morbid process complicated by prolonged rehabilitation, recurrent tendon rupture and persistent loss of motion.

Table 3. Treatment-related adverse events.

Adverse event	Treatment patients reporting adverse event (n = 1082)	Placebo patients reporting adverse event (n = 137)
Peripheral edema	833 (77.0%)	7 (5.1%)
Contusion	590 (54.6%)	4 (2.9%)
Injection site pain	440 (40.7%)	13 (9.5%)
Pain in extremity	394 (36.4%)	5 (3.6%)
Injection site hemorrhage	373 (34.5%)	4 (2.9%)
Tenderness	309 (28.6%)	0 (0%)
Injection site swelling	266 (24.6.%)	7 (5.1%)
Ecchymosis	196 (18.1%)	0 (0%)
Pruritis	135 (12.5%)	1 (0.7%)
Skin laceration	131 (12.1%)	0 (0%)
Lymphadenopathy	119 (11.0%)	0 (0%)
Blood blister	97 (9.0%)	0 (0%)
Axillary pain	73 (6.7%)	0 (0%)
Hematoma	60 (5.5%)	NR
Injection site pruritis	56 (5.2%)	0 (0%)
Erythema	48 (4.4%)	0 (0%)
Injection site vesicles	48 (4.4%)	1 (0.7%)
Arthralgia	43 (4.0%)	2 (1.5%)
Lymph node pain	40 (3.7%)	0 (0%)
Pain	40 (3.7%)	NR
Joint swelling	37 (3.4%)	0 (0%)
Nasopharyngitis	36 (3.3%)	10 (7.3%)
Swelling	34 (3.1%)	NR
Headache	30 (2.8%)	5 (3.6%)
Dizziness	24 (2.2%)	NR
Edema	26 (2.4%)	NR
Blister	26 (2.4%)	NR
Tendon rupture	3 (0.3%)	NR
CRPS	1 (0.1%)	NR

CRPS: Complex region pain syndrome; NR: Not reported.

Long-term complications

Dupuytren's disease is characterized by recurrence and disease progression irrespective of the treatment method. Recurrence and progression represent the primary barrier to the durable, effective treatment of Dupuytren's disease. Disease recurrence following palmar fasciectomy ranges from 41–54% at 5 years [43–46] and 15% of these patients will require reoperation to address disease recurrence [45]. Disease recurrence rates following percutaneous aponeurotomy have not been definitively established; however, recurrence rates appear to be in the range of 50–60% [47]. Recurrence in the setting of collagenase injection appears comparable to that quoted for percutaneous aponeurotomy and may be somewhat higher than data published for open fasciectomy. Further investigation is required to establish the long-term efficacy of collagenase clostridium histolyticum for the treatment of Dupuytren's disease.

Collagenase clostridium histolyticum is currently under postmarket surveillance and a risk evaluation and mitigation strategy remains in

effect. This plan requires analysis of all serious adverse events, including tendon ruptures, hypersensitivity and anaphylaxis, and involves reporting on the status of healthcare-provider education and training in appropriate drug administration. Currently, collagenase is only available to physicians who have completed focused training in drug dosing and injection technique.

Clinical application & indications

Dosage & injection technique

Collagenase clostridium histolyticum has been approved by the FDA and EMA for the treatment of Dupuytren's contracture and is marketed in the USA under the trade name Xiaflex and in Europe under the trade name Xiapex. Collagenase clostridium histolyticum is supplied as a lyophilized powder. Each vial contains 0.9 mg of collagenase clostridium histolyticum and is reconstituted with sterile diluent consisting of 0.3 mg/ml of calcium cloride dihydrate and 0.9% sodium chloride. For MCP joint contractures 0.39 ml of sterile diluent is utilized for reconstitution and a total volume of 0.25 ml is injected into the associated cord. For PIP joint contractures 0.31 ml of sterile diluent is utilized for reconstitution and a total volume of 0.20 ml is injected into the associated cord. Once reconstituted, clostidial collagenase may be stored at room temperature for 1 h or refrigerated for up to 4 h.

Injection is performed with a 1-ml syringe and a 0.5-inch, 27-guage needle. The practitioner's nondominant hand is use to apply gentle extension to the finger undergoing injection. This extension force is critical in displacing the cord superficially within the palm, away from the underlying flexor tendon mechanism. The needle is inserted through the skin in a perpendicular fashion into the underlying cord. The tissue should be firm and resist easy passage of the needle. Passive manipulation of the DIP joint ensures that the needle has not been improperly positioned within the underlying flexor tendon. One-third of the injection is performed. The needle is then repositioned 2–3 mm distal without fully withdrawing the needle tip from the skin. Proper positioning is confirmed and one-third of the dose is administered. The needle is then repositioned 2–3 mm proximal to the initial injection and the final one-third of the dose is administered. MCP contractures should be injected at approximately the level of the palmar crease while PIP contractures should be injected just distal to the palmodigital crease. Care should be taken to avoid injection more than 4 mm distal to the palmodigital crease as injection in this region maintains a higher risk of intertendinous injection. The patient is then placed in a soft, bulky dressing and instructed to maintain hand elevation. Local anesthesia is not recommended at the time of injection due to distortion of the soft tissue anatomy and in order to obviate the risk of intraneural injection (Figure 2).

Manipulation is performed 24 h following injection. Digital or wrist blocks may be utilized at the time of manipulation to facilitate patient comfort. Manipulation of MCP joint contractures is performed by applying gentle passive extension, holding the finger in maximal extension for 10–20 s. Up to three attempts may be performed. Manipulation of PIP joint contractures is performed by placing the MCP joint in flexion prior to application of gentle, passive extension across the PIP joint. Patients are then placed in nighttime extension splinting for 4 weeks and instructed in passive extension exercises. No splint is worn during the day and patients often return to active use of the hand within 3–5 days depending on comfort. This protocol is in contrast to the more conservative immobilization and range of motion protocols tolerated by patients undergoing open fasciectomy who typically remain immobilized for 7–10 days and have limited use of the operated hand for 4–6 weeks. Only a single cord may be injected at one time. Repeat dosing may be performed at 4 weeks to address contracture unresponsive to initial injection. A total of three injections may be performed for a single Dupuytren's cord.

Traditionally accepted operative indications include MCP joint contracture of 30° or more and any degree of PIP joint contracture as these degrees of deformity are generally considered functionally limiting. Definitive indications for collagenase clostridium histolyticum injection have not, as yet, been clearly established and it is reasonable to extrapolate well-established operative indications as a basis for nonoperative treatment. Over time it is quite likely that indications for injection will broaden as experienced practitioners begin to utilize collagenase in patients with less severe contracture.

Collagenase also maintains a viable role in patients who are not generally considered operative candidates due to inability to tolerate a general anesthetic, sedation or regional anesthesia required to perform an open operation. Clostridial collagenase may also be utilized as

a presurgical adjunct in patients whose contracture is so severe as to preclude access to the palm. Ideal candidates for collagenase injection must have a distinctly palpable cord and corollary joint contracture. MCP joint contractures are technically easier to treat than PIP joint contractures as the pretendinous cord is generally distinctly palpable at this level and the neurovascular bundle remains deep to the fascial structures.

Conclusion

Collagenase clostridium histolyticum represents the first commercially available, clinically efficacious option for the nonoperative treatment of Dupuytren's disease. It is clear that neither collagenase injection, nor percutaneous fasciotomy or open fasciectomy, provide a cure for Dupuytren's disease. Disease recurrence and progression are to be expected irrespective of the treatment path chosen; however, these interventions differ with respect to ease of treatment, periprocedural course, inherent risk of intervention, complications and durability of the correction. These are the factors that must be considered by both the treating physician and the patient.

Phase II and III clinical trials of collagenase clostridium histolyticum have demonstrated relative safety in the hands of well-trained physicians with a clear understanding of the anatomy and pathoanatomy of Dupuytren's disease. Although minor complications associated with injection are common, major complications including complex region pain syndrome and flexor tendon rupture are rare and occur at rates comparable to those observed in open fasciectomy. The adverse outcome of flexor tendon rupture deserves particular attention and vigilance as this injury is functionally devastating and requires staged flexor tendon reconstruction for rehabilitation. Patients must understand this risk and practitioners must appreciate the implications of tendon rupture and reconstruction prior to incorporating collagenase injection into their practice.

The exact role of collagenase clostridium histolyticum in the treatment algorithm for Dupuytren's disease is not yet definitively established and will continue to evolve over the course of the next decade. Currently, patients with multiple or severe contractures and those with recurrent disease are ideal candidates for open fasciectomy, while those with isolated contractures of moderate severity are candidates for either percutaneous fascioctomy or collagenase injection. The relative advantages and disadvantages

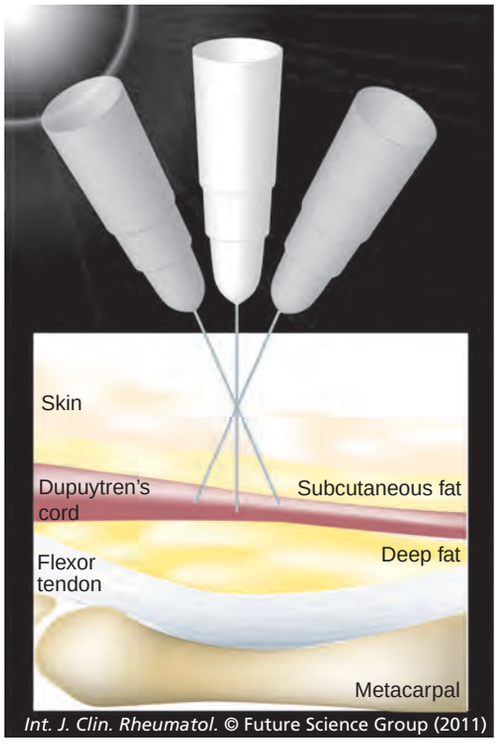

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Figure 2. Injection technique.

of collagenase injection versus percutaneous fasciotomy remain speculative. Further delineating the role of collagenase clostridium histolyticum and defining the safety and efficacy profile in general clinical practice will provide avenues for further research. To date, injection protocols in all studies have been carried out by fellowship-trained hand surgeons, instructed in proper injection technique. Familiarity with the surgical anatomy of Dupuytren's disease and formal training has likely mitigated many of the potential complications of collagenase clostridium histolyticum injections. Postmarketing surveillance will provide an accurate assessment of the efficacy and safety profiles as the drug is administered by a broader group of practitioners.

Future perspective

As practitioners become more familiar with collagenase clostridium histolyticum injection, the indications for injection will most likely expand. Current indications are reflective of surgical practice. These indications are based on the relative risk of open surgical intervention in relation to the functional limitations imparted by the degree of contracture. Over time, the indications for collagenase injection will evolve to reflect the balance between the relative risk of injection in relation to the functional limitations imparted by the degree of contracture. Clostridial collagenase injection

may play a role in the treatment of lesser degrees of contracture and may potentially forestall the need for operative intervention. Application to multiple, simultaneous contractures will likely occur, particularly in patients who seek to avoid surgical intervention. Internet use is also likely to result in an increase in the number of patients searching for practitioners willing and capable of administering collagenase treatment.

Additional clinical application for collagenase clostridium histolyticum will also continue to evolve over time, as abnormal collagen deposition is a critical component in a multitude of musculoskeletal and cutaneous pathologies. Investigation regarding the utility of collagenase in the treatment of adhesive capsulitis of the shoulder is ongoing and additional utility in the treatment of joint contracture and scar formation are potential future avenues of inquiry.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Executive summary

Mechanism of action

- Collagenase clostridium histolyticum is a fixed-dose mixture of class I (Aux I) and class II (Aux II) collagenase isoforms that act in concert to degrade collagen.
- Class I collagenase degrades the triple-helical structure of intact collagen, primarily at the N- and C-terminal domains.
- Class II collagenase degrades denatured collagen and internal peptide sequences.
- Type IV collagen (component perineurium and vessel adventitia) is relatively spared by this combination of collagenase isoforms.

Pharmacokinetic properties

- The degradative effects of collagenase clostridium histolyticum are confined to the region of injection.
- Injected collagenase is inactivated at the site of injection within 24 h of administration.
- Systemic volume of distribution and metabolism studies have not been conducted.

Clinical efficacy

- Reliable correction of metacarpophalangeal and proximal interphalangeal joint contracture in the setting of Dupuytren's disease has been demonstrated in Phase II and Phase III clinical trials.
- Collagenase clostridium histolyticum provides an alternative treatment to open surgical fasciectomy and percutaneous aponeurotomy.
- Long-term efficacy and recurrence rates are yet to be established.

Safety & tolerability

- A detailed appreciation of palmar and digital fascial anatomy and pathoanatomy is paramount in the successful treatment Dupuytren's cords with clostridial collagenase and necessary for the avoidance of treatment-related complications.
- Minor treatment-related adverse events including pain with injection and manipulation, swelling, erythema and adenopathy are common.
- Serious treatment-related adverse events are rare and include flexor tendon rupture and complex region pain syndrome.

Drug interactions

- The tetracycline family of antibiotics has been shown to inhibit matrix metalloproteinase-mediated collagen degradation *in vitro* and may present a potential, although unproven, interaction.

Drug dosage & administration

- Collagenase clostridium histolyticum is administered as a 0.58-mg dose directly injected into the Dupuytren's cord.
- Manual manipulation should be performed 24 h after initial injection.
- Repeat injection may be performed at 4 weeks with up to three doses administered per cord.

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