Collagenase clostridium histolyticum for Dupuytren’s contracture

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**Importance of the field:** Dupuytren’s disease is a non-malignant, progressive disorder of the hands that can severely limit hand function and diminish overall quality of life. With global life expectancy increasing, the prevalence of this disease appears to be increasing amongst all ethnic groups. Treatment has traditionally remained surgical with few effective, nonsurgical options. However, with the introduction of collagenase clostridium histolyticum to treat Dupuytren’s contractures, physicians and surgeons may be provided with a new, office-based, non-surgical option to treat this disease.

**Areas covered in this review:** The literature behind the use of collagenase to treat Dupuytren’s disease; including its mechanism of action, safety, efficacy and clinical evidence behind its recent FDA approval.

**What the reader will gain:** The latest information available on collagenase through a comprehensive review of PubMed and the websites of licensing organizations for medicinal products.

**Take home message:** Phase III, clinical trials on collagenase for treatment of Dupuytren’s contractures have recently been completed. Meeting primary and secondary objectives, collagenase has obtained FDA approval for clinical use. Collagenase now provides a non-operative option for Dupuytren’s disease. Although short-term results show that collagenase is safe and efficacious, long-term effects of repeat injections and contracture recurrence rates have yet to be examined.

**Keywords:** collagenase injections, Dupuytren’s disease, enzymatic fasciotomy, hand contractures

**1. Introduction**

Dupuytren’s disease is a benign connective tissue disorder affecting the palmar fascia leading to slowly progressive contractures involving the hands. Although the exact etiology is still not fully understood, previous studies have shown that the process involves abnormal myofibroblast-mediated collagen deposition in the palm leading to the formation of pathologic cords. Over time, these cords contract leading to progressive flexion deformity of the fingers involving the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, but can also involve the distal interphalangeal (DIP) joint. The ring and small finger are most commonly involved.

Global prevalence of Dupuytren’s disease varies from 2 to 42% with a much higher incidence in older men of northern European descent. The inheritance pattern appears to be autosomal dominant with variable penetrance [1]. Men appear to be six times more likely to be affected than women and usually present 10 years earlier. The incidence increases with advancing age in both males and females across all ethnic groups.
Initially described by Platter, in 1614, surgical intervention traditionally has been the most effective and widely accepted treatment for progressive Dupuytren’s contractures [2,3]. Numerous non-surgical interventions tried over the years including physical therapy, corticosteroid injections, dimethylsulfoxide injections, topical vitamin A and E and gamma interferon injections have largely been found to be ineffective and clinically not adopted [4]. In the 1960s, Bassot described a technique using injectable enzymatic compounds into diseased cords allowing for their degradation and subsequent rupture [5]. A few years later, Hueston coined this technique as enzymatic fasciotomy and used a mixture of trypsin, hyaluronidase and lidocaine [6]. Using a similar technique, McCarthy reported long-term results that showed similar recurrence rates between enzymatic fasciotomy and surgical fasciectomy, but also reported a higher rate of complications associated with the enzymatic technique [7,8].

The use of collagenase clostridium histolyticum (Box 1) as a potential minimally-invasive, non-surgical option to treat Dupuytren’s contractures has led to completion of Phase III clinical trials and its recent FDA approval for clinical use. Initially discovered in the media of cultured Clostridium histolyticum over 50 years ago [7], collagenase was introduced to the literature as a potential treatment option for Dupuytren’s disease less than 15 years ago [8]. When injected into the Dupuytren’s cord, collagenase from Clostridium histolyticum leads to lysis of collagen found within the diseased tissue. This has been successfully administered in an office-based setting without the need for anesthesia. The patient returns the following day for a manipulation of the involved joints in an attempt to rupture the cord. Results from Phase III clinical trials report that collagenase use is safe and efficacious when used within the appropriate guidelines; however, long-term results and recurrence rates are currently not available [9-12].

### Box 1. Drug summary.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Collagenase clostridium histolyticum</th>
</tr>
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<tbody>
<tr>
<td>Phase</td>
<td>Phase IV: post-marketing surveillance</td>
</tr>
<tr>
<td>Indication</td>
<td>Dupuytren’s contracture with palpable cord in adult patients</td>
</tr>
<tr>
<td>Pharmacology description</td>
<td>Lyses collagen triple helix structure</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Injected subcutaneously, directly into cords</td>
</tr>
<tr>
<td>Pivotal trials</td>
<td>CORD I Trial [9,10-13]</td>
</tr>
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3. Chemistry

3.1 Collagenase clostridium histolyticum

Since its discovery by Maclellan in 1953, collagenase clostridium histolyticum has been extensively described in the literature for numerous clinical and research applications. Clostridium histolyticum collagenases are metalloprotease enzymes of the matrixin subfamily. Two separate chromosomal genes, colG and colH control homologous expressions of these enzymes. Seven different enzymes have been isolated by proteolytic cleavage of the COOH terminus of the terminus colG and colH full length gene products. Collagenases are categorized into one of two classes based on gene of origin, protein domain and substrate specificity (Table 1) [20-22]. Currently, the only commercially available injectable Clostridium histolyticum collagenase for Dupuytren’s disease has recently obtained FDA approval for clinical use and is marketed under the name Xiaflex® (Auxilium Pharmaceuticals, Inc.). This compound, isolated from the culture medium of Clostridium histolyticum, comprises a fixed-ratio mixture of a clostridial type-I collagenase (known by the manufacturer as AUX-I) and a clostridial type-II collagenase (AUX-II). The type-I collagenase is a single polypeptide chain containing approximately 1000 amino acids of known sequence and with a molecular weight of 114 kDa. The type-II collagenase is also approximately 1000 amino acids long and has a molecular weight of approximately 114 kDa.

Prior to the introduction of Clostridium histolyticum collagenase, there were no commercially available injectable or parenteral medications to treat Dupuytren’s disease. Treatment of these hand contractures has historically remained surgical. Surgical options included a limited needle aponeurectomy, percutaneous versus open fasciectomy and the more commonly performed, open fasciectomy. These surgical interventions can be complicated and both intraoperative and postoperative complications, such as nerve injury, arterial injury, wound infection, scar contracture, loss of function and rarely flexor tendon injury can occur [10-15]. Despite these treatment options, recurrence or extension is the rule rather than the exception [16]. Post-operative recovery can also be prolonged depending on the treatment chosen [16,17]. Surgery is recommended in patients with metacarpophalangeal (MCP) joint contractures of at least 30 degrees and/or any proximal interphalangeal (PIP) joint contractures with associated functional impairment [18].

The use of collagenase for the treatment of advanced Dupuytren’s disease is the first attempt to provide physicians with a novel biologic alternative to surgery. Although population studies have shown significant variability in the prevalence of this disease, it is genuinely accepted that the incidence rises with increasing age. This is especially true with men entering their fifth decade and women entering their sixth decade of life [2,19]. Many of these patients have associated comorbidities, which makes surgical intervention associated with higher risk. The option of a non-operative modality may be appealing for this patient population, if it can be shown to have overall less risk. If risk and recurrence rates can be shown to be sufficiently low, then collagenase-induced enzymatic fasciectomy can be considered as first-line treatment for progressive hand contractures.
enzymes lyse the normal collagen structure within the cord III collagen, not usually seen in adult palmar fascia. These amount of type I collagen and an unusual amount of type cords, its enzymatic activities specifically target the collagen effect of
3.2 Pharmacodynamics
acting alone [20]. Class-I and class-II collagenase work synergistically and were conducted by the manufacturer, claim that this combination of molecule. Their substrate activity patterns are representative of domain structure, substrate affinity, catalytic efficiency and preferred cleavage site on the collagen each other in terms of domain structure, substrate affinity, catalytic activity against collagen, each enzyme molecule requires active catalyst and collagen-binding domains. In addition, these enzymes require both calcium and zinc to act as metal cofactors to facilitate the enzymatic process [20]. Zinc is required for activation at the catalytic site and calcium is essential to maintain the appropriate structure of the collagen-binding site to accept the triple-helix structure of the collagen fibrils [23]. By injecting collagenase directly into Dupuytren’s cords, its enzymatic activities specifically target the collagen within the diseased cord. These cords have an abundant amount of type I collagen and an unusual amount of type III collagen, not usually seen in adult palmar fascia. These enzymes lyse the normal collagen structure within the cord and make them more susceptible to rupture [8,24]. Both classes of collagenase are not immunologically cross-reactive and have broad catalytic effects on all collagen types, except for type IV. This information may be clinically beneficial because type IV collagen is found in the basement membranes of blood vessels and perineurium of peripheral nerves. Non-clinical studies failed to show significant degradation of blood vessels, nerves and epithelia following local injection and may be related to its poor activity against type IV collagen [7,25,26].

Pre-clinical, animal studies have found no detectable systemic effects following intravenous injection of collagenase. This has also been supported with clinical trials that have not shown any detectable levels of collagenase systemically once injected subcutaneously [9,27]. As a result, clinical drug interaction studies have not been conducted. Although not clinically evaluated, the tetracycline family of antibiotics has shown to inhibit matrix metalloproteinase-mediated collagen degradation in published in vitro experiments [18,28]. This interaction may be related to the local chelation of the metal cofactors essential for collagenase activation. Clinically, these antibiotics could theoretically inhibit collagenase activity, if taken together [20]. Secondary pharmacologic effects of collagenase may be attributed to its primary pharmacodynamic activity, collagen cleavage. These major secondary effects have been identified in vivo as vascular leakage, neutrophil (PMN) chemotaxis and wound healing responses, and are indirectly related to collagenase activity. Localized edema and hemorrhage at the site of injection is seen clinically after administration of collagenase [9,27,29]. Investigational studies have shown that potent bradykinnin-like effects causing degranulation of local mast cells in the surrounding capillaries may mediate this [30]. Transient neutrophil chemotaxis is seen in vivo (animal models) and may be attributed to the byproducts associated with collagen breakdown. These effects have yet to be seen as clinically significant. Animal studies have also shown that early changes seen within 24 h at the injection site showed increased numbers of fibroblasts and neo-capillary formation. This fibroproliferative process is characteristic of an early wound healing response [25,26].

3.3 Pharmacokinetics and metabolism
Clinical absorption studies of collagenase after injection have been conducted to determine the pharmacokinetics of this compound. The results of both published and unpublished studies have shown that collagenase is not absorbed in high concentration immediately after injection or after the subsequent procedure involving cord rupture. A limited study evaluating the elimination of collagenase was conducted on four patients by obtaining urine samples after various time periods after a 10,000 U injection. According to published results, an estimated 7 to 28% of the collagenase was recovered [13]. Most of the recovery was seen in the 30 and 60-min time samples.

Table 1. Characteristics of class I and class II clostridial collagenases.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Class I characteristic</th>
<th>Class II characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene of origin</td>
<td>colG</td>
<td>colH</td>
</tr>
<tr>
<td>Subtypes in class</td>
<td>α, β, γ and η</td>
<td>δ, ε and ζ</td>
</tr>
<tr>
<td>Affinity for intact collagen</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Collagen binding domain structure</td>
<td>Tandem domains (S3a &amp; S3b)</td>
<td>Single domain (S3)</td>
</tr>
<tr>
<td>Preferred cleavage sites</td>
<td>N and C termini</td>
<td>Internal peptide sequences</td>
</tr>
<tr>
<td>Preferred substrate(s)</td>
<td>Triple helical (intact) collagen</td>
<td>Small peptides &gt; denatured collagen (gelatin) &gt; triple helical (intact) collagen</td>
</tr>
</tbody>
</table>

This data may suggest the ability of the kidneys to concentrate and excrete collagenase after injection. However, direct elimination studies could not be conducted because detectable levels of serum collagenase were not seen in these studies. Previous work, where detectable levels of serum collagenase were seen, described that enzyme inactivation occurred with binding to endogenous serum components. The liver eventually eliminates these enzyme-inhibitor complexes.

Tissue distribution studies have not been conducted because no significant systemic exposure was seen in human subjects after injection. This indicates that the collagenase remains relatively confined to the localized tissues after injection. Clostridiom histolyticum collagenase does not require proteolytic cleavage to be activated and functions in its native form. Collagenase is not a substrate for drug metabolizing pathways such as cytochrome P450 and metabolism studies have also not been conducted. In vitro studies have shown that most collagen digestion was completed by 24 h after exposure to collagenase [8,20].

### 3.4 Non-clinical studies

Since its initial discovery over 50 years ago, Clostridium histolyticum collagenase has been well studied in vitro and in vivo, in animal models. Although the drug’s manufacturer has conducted numerous unpublished studies, this review will focus on published studies directly leading to its use in Dupuytren’s disease. The effects of collagenase in human tissue are based on initial studies looking at Peyronie’s disease. Collagen digestion involving human tissue was studied in vitro using surgical specimens of Peyronie’s plaques and normal human albuginea. After being injected with 400 units of Clostridial collagenase, the specimens were later analyzed after a 24-h incubation period. Both tissue types have shown to have lost between 80 and 99% of their original weight, signifying their high collagen content. A collagenase dose–response study on pericardial tissue showed a defined area of collagen lysis, which correlated with the dose injected. The focus of collagen lysis did not expand beyond the confines of the initial injection. Histologic studies on these specimens showed no degradation of elastic tissue and no structural damage to the nerve fibers and arteries/arterioles; however, there was some dissolution of the perineurium and breakdown of small venules [31].

Starkweather et al. [8] reported the first in vitro experiments on actual Dupuytren’s cords excised from patients undergoing fasciectomy. This study focused on determining the clinical dose range of collagenase needed for clinical utility, defining the minimal effective dose needed to cause complete cord rupture and to quantify the extensive force required to allow for cord rupture. This results of this study showed that by injecting excised cord to high dose of collagenase (3600 U) there was a 93% decrease in tensile modulus when compared with the controls and lead to a complete disruption of the cord in 3 of the 10 specimens in the experimental group. The dose response study (150, 300 and 600 units) showed a significant decrease in stress to failure with increasing collagenase dose. It was determined from this study that a minimum effective dose of 300 units was needed to cause cord rupture within normal extension force. Histologic analysis of these excised cords after injection also showed increasing collagen lysis with increasing collagenase dose.

Another non-clinical study conducted on rat tail tendon by the same group, involved injection of 150 and 300 units of collagenase to determine tissue extravasation up to 24 h after injection. They found that no adverse tissue extravasation occurred at any time points tested and no collagen lysis was seen beyond 0.5 cm proximal and distal to the injection site in both dose-response groups [24].

### 3.5 Clinical studies

Collagenase has been used clinically for numerous applications prior to its introduction to treat Dupuytren’s disease. The use of collagenase to treat severe burns and leg ulcers was described nearly 40 years ago [32]. As with the non-clinical trials, clinical trials involving collagenase were first conducted in Peyronie’s disease. In clinical trials conducted...
significant immune response (including anaphylaxis) would be unlikely [35].

Prior to its approval by the FDA a total of 13 clinical trial (one Phase I, three Phase II and nine Phase III) have been conducted in Europe, Australia and the USA [20]. Funded in large part by the drug’s manufacturer, the results of these trials have lead to the collagenase’s recent approval. However, many of these trial results have failed to reach the literature and undergo peer-reviewed scrutiny. This review will again focus only on published, clinical studies leading to its use in Dupuytren’s disease.

Badalamente and Hurst [29] presented the first clinical study involving collagenase injections in patients with Dupuytren’s contracture. Phase I of their study involved a dose titration into cords causing MCP joint contracture to determine the amount of collagenase needed for cord rupture. After starting at 300-units, a number they obtained from the in vivo animal study mentioned above, they found that a dose of 10,000-units of collagenase was necessary to allow for cord rupture. This dose was then used in their Phase II open-label trial. A total of 29 patients, including 34 MCP joint, 9 PIP joints and 1 thumb cord were enrolled and had collagenase injections. Ultrasound was used to verify the depth from the skin to the flexor tendon sheath, but was not used to guide actual injections (Figure 2). Patients were seen the following day, when a passive extension force was applied to rupture the cord. Patients where sent home in a night-extension splint and instructed to do extension exercises for a total of four months. In order to obtain a joint angle corrected to 0 – 5°, 15 patients required multiple injections with one patient receiving a maximum of six injections. A total of 82% (28 of 34) of MCP joints obtained full extension with full range of motion. The patient who underwent six injections ultimately failed and underwent palmer fasciectomy. There were a total of three recurrences in 2 years after initial correction. Four out of nine of cords (44%) causing PIP joint contractures achieved full extension and full range of motion. One patient corrected to within 10° of full extension and two corrected to within 15°. Two patients with PIP joint contractures ultimately failed and went on to surgery. The patient with a thumb cord corrected from 45° to 10°. There were no reported major adverse reactions, but minor adverse reactions were limited to local tenderness and edema. Six patients experienced forearm tenderness with elbow and axillary lymphadenopathy which resolved within 1 – 2 weeks. There were no reported tendon ruptures in this series. Serum antibody titer to collagenase were conducted and found to be positive in 13 of the 15 patients who had multiple injections. These titers decreased over time.

The results of the above open-label trial led to the randomized, double-blinded, placebo controlled trial (Phase IIA) [13]. This trial involved a single dose injection of 10,000-units of collagenase versus placebo. A total of 36 patients with isolated MCP joint contractures and 13 patients with isolated PIP joint contractures. A similar protocol as mentioned in the previous study was used; however, as the study progressed, pre-injection ultrasounds were no longer conducted. The results of the MCP joint correction after injection showed that at 1 month showed that 14 of 18 patients in the collagenase group achieved full extension as opposed to 2 of 18 in the placebo group (p = 0.001). The four patients who failed to achieve full correction after the first injection, achieved full correction by the second injection. The 16 of 18 patients in the placebo group, who failed to reach full correction, were later treated with collagenase with correction of 10 patients with one injection, two patients with two injections and one patient with three injections. Three patients in the placebo group failed to correct even with collagenase injections. In the PIP contracture group, five of seven patients corrected with one injection of collagenase, 1 corrected after two injections and 1 ultimately failed to correct. All six patients in the PIP contracture group that received placebo failed to correct. The adverse reactions seen in this trial includes localized tenderness, edema and pain after cord rupture. One-third of patients developed lymphadenopathy, which resolved without consequence. A few patients with severe contractures developed skin tears after cord rupture. Out of 36 patients 26 had serum titers of immunoglobulin E against collagenase. In this study, one patient developed hives after receiving six injections of collagenase. In addition, a clinical dose–response study (Phase IIB) [27] was conducted to determine the minimal safe, efficacious dose required for cord rupture. This trial enrolled 80 patients with either MCP joint or PIP joint contracture and split them into four groups receiving different doses of collagenase with each injection. Overall, the results of this trial showed that the 10,000-unit collagenase injection was the minimal safe and effective dose.

The findings of the Phase II clinical trials led to the approval to proceed with Phase III clinical trials. Badalamente and Hurst [36] reported the results of a Phase III double-blind, placebo-controlled trial followed by an open-label phase. This study had a follow-up period of up to 12 months after the last injection. A total of 35 patients were enrolled and 33 patients completed the study. In the double-blind portion of this study, 16 of 23 patients corrected (< 5° of flexion) with one injection and additional five patients corrected after three injections. An average of 1.5 injections were needed for correction. In the open-label phase of the study, 17 of 19 patients (from the placebo group) achieved success after an average of 1.4 injections. In this study, 62 joints (31 MCP, 31 PIP) were treated in 35 patients and 54 of these joints achieved clinical...
Collagenase clostridium histolyticum

Figure 2. Collagenase being injected into a cord in a patient with Dupuytren’s disease.

success. Five joints had a re-occurrence with a 24-month period. There were no reported major adverse events in this study. Local reaction to the injection was found to be the most commonly reported complication.

The reported outcomes of these earlier trials led to the large, multi-center, prospective, Phase III clinical trial. Known as the Collagenase Option for Reduction of Dupuytren’s (CORD) I study [9], this trial was a 90-day, randomized, double-blind, placebo-controlled study with an ongoing open-label extension. Enrollment involved 308 patients with Dupuytren’s joint (MCP and/or PIP) contracture of 20 degrees or greater from 16 participating centers. Patients initially received injections and returned the following day for joint manipulation to try to rupture the injected cord. The injections were limited to three per cord and total of 741 injections (444 collagenase and 297 placebo) were administered. The results of this study showed that 64% of joints injected with collagenase versus 6.8% injected with placebo corrected to within 5° of extension or less (p < 0.001). The average reduction of joint contracture 30 days after last injection was from 50.2° to 12.2° in the collagenase group and from 49.1° to 45.7° in the placebo group (p < 0.001). MCP joint contractures appeared more likely to correct and corrected to a more significant degree when compared with PIP joint contractures. Adverse events were seen in 96.6% of patients who received collagenase versus 12.2% of patients in the placebo group. Most of these events were local reactions to the injection, which included peripheral edema, contusion, injection-site hemorrhage, pain, tenderness and pruritus; however, there were three treatment-related, major adverse events in the collagenase group. These included one patient who developed complex regional pain syndrome and two patients with flexor tendon ruptures. These tendon injuries were considered to be due to collagenase being injected within the tendon sheath. Two patients discontinued treatment in the collagenase group due to severe injection-site pain after the first injection in one patient and prolonged dizziness after the first injection in another patient. There were no reported digital nerve or artery injuries. Although most patients (> 85.8%) tested positive for antibodies against type I (AUX-1) and/or type II (AUX-2) collagenase 30 days after the first injection and all tested positive after a third injection, there were no significant systemic, allergic reaction reported in this study population.

The results of these Phase III trials combined with the other previous studies were submitted for FDA approval. On February 2, 2010, collagenase clostridium histolyticum was approved for the treatment of adult patients with Dupuytren’s contracture with a palpable cord [37]. Currently, collagenase is currently in its post-marketing surveillance phase. Due to some sequence homology, the FDA has required that the manufacturers of Clostridium histolyticum collagenase (Xiaflex) conduct studies to determine if anti-collagenase antibodies to type I and type II collagenase (AUX-1 and AUX-2) have any potential cross-reactivity to endogenous human matrix metalloproteinases. This may lead to potential inhibition of endogenous enzyme activity. Other studies to be conducted in the post-marketing surveillance phase include an in-depth look into the AUX-1 and AUX-2 intermediates, testing container-closure integrity, product quality and purity testing. The FDA has also approved a Risk Evaluation and Mitigation Strategy (REMS) assessment plan, which requires a special analysis of all serious adverse events, especially tendon ruptures, hypersensitivity reactions and anaphylaxis. This also involves reporting on the status of healthcare provider education and training in appropriately delivering the drug.

3.6 Safety and tolerability

The safety of Clostridium histolyticum collagenase in Phase I, Phase II and Phase III clinical trials (both published and unpublished studies) were combined and reported to the FDA [20]. A total of 2630 injections of collagenase were used to treat 1780 cords in 1082 subjects with Dupuytren’s disease. Greater than 25% of these patients experienced an adverse local event such as peripheral edema, contusion and injection site pain (Table 2) [20]. The major, treatment-related events included three patients with tendon ruptures, one patient who developed complex regional pain syndrome, one patient who developed tenonitis, one patient who developed a finger deformity and one patient with a pulley injury. Over 85% of patient developed anti-collagenase antibodies after one injection of collagenase and nearly all patients developed antibodies after three injections; however, no reported cases of systemic hypersensitivity reactions or anaphylaxis was seen across these studies. There was also no notable correlation between antibody titers and the degree, rate and/or severity of adverse events.

Safety regulations have been set up by the drug’s manufacturer to decrease risk of adverse events and have submitted distribution guidelines to the FDA [20]. The product,
Table 2. Percentage of patients with adverse events after receiving 1 or more injections of collagenase (first dose of collagenase to 30 days post-last dose).

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Collagenase Clostridium histolyticum 0.58 mg (n = 1082) n (%)</th>
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<tbody>
<tr>
<td></td>
<td>All adverse events</td>
</tr>
<tr>
<td>Number (%) of subjects</td>
<td>1061 (98.1)</td>
</tr>
<tr>
<td>with ≥ 1 AE</td>
<td></td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>833 (77.0)</td>
</tr>
<tr>
<td>Contusione</td>
<td>590 (54.6)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>440 (40.7)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>394 (36.4)</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>373 (34.5)</td>
</tr>
<tr>
<td>Tenderness</td>
<td>309 (28.6)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>266 (24.6)</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>195 (18.1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>132 (12.5)</td>
</tr>
<tr>
<td>Skin laceration</td>
<td>131 (12.1)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>119 (11.0)</td>
</tr>
<tr>
<td>Blood blister</td>
<td>97 (9.0)</td>
</tr>
<tr>
<td>Axillary pain</td>
<td>73 (6.7)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>60 (5.5)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>56 (5.2)</td>
</tr>
<tr>
<td>Erythema</td>
<td>48 (4.4)</td>
</tr>
<tr>
<td>Injection site vesicles</td>
<td>48 (4.4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>43 (4.0)</td>
</tr>
<tr>
<td>Lymph node pain</td>
<td>40 (3.7)</td>
</tr>
<tr>
<td>Pain</td>
<td>40 (3.7)</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>37 (3.4)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>36 (3.3)</td>
</tr>
<tr>
<td>Swelling</td>
<td>34 (3.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>30 (2.8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>24 (2.2)</td>
</tr>
<tr>
<td>Edema</td>
<td>26 (2.4)</td>
</tr>
<tr>
<td>Blister</td>
<td>26 (2.4)</td>
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*Clostridium histolyticum* collagenase, will be targeted to physicians familiar with Dupuytren’s disease (i.e., hand surgeons, orthopedic surgeons, plastic surgeons and rheumatologists). Physicians wishing to deliver collagenase will need to complete a clinical training program, which includes an injection training video and/or manual, and attest to its completion prior to receiving the product. These regulations were created to avoid inadvertent injection of collagenase into vital collagen-containing structures (i.e., tendon and ligaments).

### 4. Conclusion

Until *Clostridium histolyticum* collagenase’s recent approval by the FDA, patients and the physicians who treat them have long been frustrated by a lack of nonsurgical options for treatment of this disease. Currently, the treatment of Dupuytren’s disease has and continues to be largely surgical. Patients wait for contractures to progress until they interfere with daily life. Traditionally, surgeons use contractures involving the MCP joint of 30 degrees or more and any contractures affecting the PIP joint as loose criteria to operate [18]. The introduction of *Clostridium histolyticum* collagenase theoretically offers a novel, office-based approach for Dupuytren’s contractures and has recently sparked notable interest in physicians and surgeons who treat patients with Dupuytren’s disease.

The role of collagenase in cord rupture is similar to the enzymatic fasciotomy initially described over 40 years ago [5,6]. Collagenase works by cleaving the triple helical structure of collagen found within the diseased cord, and thus, weakening it for rupture. This two-stage process involves initial injection of collagenase (10,000 U/dose) directly into the affected cord. Patients then return in 24 h for joint manipulation where an extension force is applied to the joint as an attempt to rupture the cord. Collagenase’s activity is not just limited to the collagen within these cords, but can affect any collagen-containing structure. As a result, collagenase can cause serious damage to tendon, ligamentous structures and articular cartilage. There were two reported tendon ruptures that occurred after collagenase injection seen in the large, multi-center study reported by Hurst et al. [9]. This was included in the grand total of three tendon ruptures seen across all studies reported to the FDA. All three of these tendon ruptures occurred after injections into the small finger. A special note of caution should be made with injections involving the small finger as the reported adverse events of boutonniere deformity and pulley injury also occurred after injections into the small finger. Surprisingly, there were no reported cases of digital nerve or arterial injury seen across all clinical trials conducted on collagenase. This may be related to findings seen in the non-clinical studies conducted on collagenase which showed that collagenase was active against all subtypes of collagen, but least active against type IV collagen. Type IV collagen is the primary subtype seen in the basement membrane surrounding neurovascular structures.

The results from the clinical trials show that there is an active immune-response seen in patients after receiving collagenase injections as indicated by the anti-collagenase antibody titer levels [10-13]. Although there was not a correlation between titer levels and adverse events, it does bring into question the effectiveness of collagenase activity with repeat injections. Also, there is potential for cross-reactivity of these antibodies to endogenous human matrix metalloproteinases and causing intrinsic, enzymatic dysfunction. Currently, post-marketing surveillance studies are being conducted to better understand this potential interaction.

Overall, collagenase has been shown to be highly effective in correcting Dupuytren’s contractures affecting MCP joint and PIP joint when compared to placebo. With an acceptably low side effect and risk profile, *Clostridium histolyticum* collagenase has recently obtained FDA approval for clinical
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use. However, long-term studies on the effects of collagenase and overall reoccurrence rates have yet to be fully conducted. In addition, no direct comparison studies have yet been conducted between collagenase and the current gold standard, palmar fasciectomy. Nonetheless, the results of these clinical trials are impressive and show significant promise. *Clostridium histolyticum* collagenase provides patients and physicians with an alternative option to treat Dupuytren’s contractures.

5. Expert opinion

Clostridial derived collagenase, now FDA-approved and marketed by Auxilium as Xiaflex™ has the potential to alter the current treatment paradigm for Dupuytren’s disease. Currently, there are two alternatives to straighten contracted fingers. The most common treatment today takes place in the operating room and involves some form of excision of the contracted fascia, performed as an outpatient, under some form of anesthesia. The benefits of this treatment include being able to visualize normal and abnormal structures in order to remove all disease tissues and avoid injury to nearby precious structures such as arteries, nerves and tendons. In addition, other structures that might be contributing to the joint contracture, such as shortened ligaments or contracted tendon sheath can be addressed. Of all the treatments for Dupuytren’s disease, surgery most predictably corrects contraction and, based on studies, has the greatest durability, that is the longest average interval between correction of contraction and recurrence of disease leading to recurrence of contracture. The potential side-effects include the disabilities associated with an operated hand, such as difficulty performing activities of daily living, and the potential for surgical complications such as infection, bleeding and hand stiffness. Injury to digital nerves is the most common avoidable complication.

Gaining popularity in the USA is a less invasive procedure, termed percutaneous needle aponeurotomy. This is typically performed in the office or minor surgical room, under local anesthesia. The surgeon palpates the contracting cord and uses the bevel of a hypodermic needle placed blindly through the intact skin to ‘saw’ through the cord, all while maintaining the cord under tension. If enough of the cord is divided, the remaining fibers will rupture and the affected joint will straighten to one degree or another. It has proven to be very effective for certain disease presentations with very notable correction of contracture. It is ineffective in other disease presentations. It is less expensive than surgery and the morbidity is much less, compared to surgery. The recognized risks of needle aponeurotomy are inherent to the technique. The cord is ‘blindly’ divided. The surgeon uses his or her knowledge of anatomy to avoid, if possible, injuring other structures with the needle. Nonetheless, digital nerves and arteries and flexor tendons are at risk for being injured. These complications seem more likely to occur when the procedure is performed by non-surgeons. Studies of durability have shown that the incidence of recurrence of contracture can be as high as 60% within 2 years.

Collagenase can be considered the chemical equivalent of needle aponeurotomy with notable exceptions. It can be used where needle aponeurotomy is, for many practitioners, felt to be unsafe, for example, where the contracting cord is closely related to the digital nerve. The various clinical trials of collagenase have clearly demonstrated that it can be safely injected into cords that lie close to or are even intertwined with the digital nerve. It is more an office-based procedure than needle aponeurotomy. It is as effective as needle aponeurotomy for some of the common disease presentations, and more effective than needle aponeurotomy for many other disease presentations, particularly those affecting the proximal interphalangeal joint. It is a safer technique than needle aponeurotomy, more rapidly learned by surgeons not experienced in needle aponeurotomy, that is it has a shorter learning curve, and, although not yet clearly established, very probably has a more durable effect than needle aponeurotomy.

There is great interest among the hand surgery community in collagenase as a non-surgical treatment for contracted fingers. There is also the sense that educated patients with Dupuytren’s disease, who very much wish to avoid surgery will create a demand for this treatment. The educational prerequisites established by the manufacturer, Auxilium do not seem to represent a notable challenge. Because this is a novel treatment, there are many issues that will be addressed as time goes by, notably, how the physician will bill for the procedure and at what level will government and private insurers pay for the procedure.

Other remaining issues include the actual incidence and rate of recurrence of contracture after collagenase injection and correction of contracture, issues related to the potential for late appearing immunological complications. Both are currently being investigated by clinical trial.

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Declaration of interest

VR Hentz is a Scientific Advisory Board Member for Auxilium Pharmaceuticals, Inc.
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