# Collagenase Injection: Journey from Bench to Current Advanced Clinical Use

14

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## Contents



## 14.1 How It Began

The eponym for Dupuytren Disease was coined because Dupuytren, a French surgeon, performed a surgery using an open transverse incision in 1831 on his coach man patient with a hand contracture. However, Dupuytren Disease was actually originally described earlier in 1614 by Felix Plater of Basel. Some reports describe Dupuytren Disease even earlier in Orkney and Iceland in the twelfth and thirteenth centuries. Interestingly, Englishman John Hunter reported that Dupuytren Disease originated in ligaments and not tendons, in 1777—the year of Dupuytren's birth. Hunter also suggested that surgical fasciotomy might be done to resolve the contractures (Elliot 1989). The introduction of collagenase for the treatment of Dupuytren Disease is a much more recent event. Doctors Hurst and Badalamente invented this therapeutic option for treating Dupuytren Disease with collagenase and have championed its development since the early 1990s (Hurst 2011).

Collagenase was known since the investigations of gas gangrene, by a German scientist E. Maschmann, in 1937 (Maschmann 1937). Ines Mandl, the first woman to earn a PhD from Polytechnic Institute of Brooklyn in 1949, then further studied this enzyme. She isolated and characterized collagenase from *Clostridium histolyticum* in 1953 (Mandl et al. 1953). In 1957 the A.B. Corporation licensed collagenase for burn debridement, and Knoll Pharmaceuticals

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managed the sales for collagenase ointment for burns. A.B. Corporation was located on Long Island and later became BTC (BioSpecifics Technologies Corp).

Dr. Hurst began studying Dupuytren Disease after his hand surgery fellowship with Robert E. Carroll, MD, at New York Orthopedic Hospital at the Columbia Presbyterian Medical Center (1978–1979). Dr. Hurst became Assistant Professor at the State University of New York at Stony Brook. As the first hand surgeon at the new University Hospital at Stony Brook, Dr. Hurst was charged with starting hand teaching, hand research, and the hand surgery clinical service. The Professor and Chair of the Orthopedic Department at the time was Roger Dee, MD., who encouraged Dr. Hurst to focus his research on Dupuytren contracture.

Shortly after Dr. Hurst arrived to Stony Brook, Marie Badalamente, PhD, joined the faculty focusing on cell biology. Together they conducted several studies designed to enhance the basic science understanding of Dupuytren Disease (Hurst et al. 1986; Badalamente et al. 1992, 1996). One study in particular looked at the myofibroblasts, ATPase, and the abnormal collagen of Dupuytren Disease (Badalamente et al. 1983). This was presented at Dr. Robert McFarlane's Canadian Colloquium on Dupuytren Disease on October 9, 1985. It was at the colloquium that Dr. Hurst and Dr. Badalamente met multiple senior Dupuytren Disease investigators including Dr. Graham Stack, Dr. DA McGrouther, Dr. Michael Flynn, Dr. John Hueston, CW Kischer, and several others. In 1987 during Dr. Hurst's Bunnell Traveling Fellowship, he lectured in Oxford on the "Kreb's Cycle" of Dupuytren Disease. This concept was later expanded by Dr. George Murrell (Murrell and Hueston 1990).

In the late 1990s, Drs. Hurst and Badalamente met Dr. Raoul Tubiana and started a collaboration with him and Dr. Caroline Leclercq, which resulted in the textbook "Dupuytren Disease," published in 2000.

Therefore, it was "on the shoulders of giants," like McFarlane, McGrouther, Stack, Tubiana, and many others, that Drs. Hurst and Badalamante continued their study of Dupuytren Disease and developed a nonsurgical treatment option. Their subsequent work on collagenase had a foundation based in basic science and clinical research. The initial work with collagenase started in 1991 and involved the development of a first in category drug as well as a new therapeutic alternative for Dupuytren contracture. In the 1980s, Drs. Hurst and Badalamente were doing research on nerve repair. Tom Wegman, CEO of BioSpecifics Technologies Corporation, approached Drs. Hurst and Badalamente in 1991 about utilizing collagenase to control the amount of fibrosis around microsurgical nerve repairs. It was quickly determined that collagenase would not be helpful in nerve repair but might be very helpful in Dupuytren Disease where removing collagen is the basic goal of treatment.

## 14.2 A Plan to Study Collagenase for Dupuytren Disease Was Started

It was well known that surgical removal of the collagen "cords" in Dupuytren Disease is an extensive surgical procedure requiring patients to undergo anesthesia in an operating room and also requires a considerable amount of hand therapy postoperatively. There was always the risk of complications, as well as high recurrence rates (Hurst 2011). In addition, patients had to account for a significant loss of time from work, as well as a temporary decrease in the ability to perform their activities of daily living. Surgery was done to improve finger extension but could be complicated by decreased flexion and grip. Drs. Hurst and Badalamente recommended a minimally invasive treatment that could be done with a collagenase injection which would disrupt the collagen cord. It seemed like an excellent concept, especially since collagenase did not cause any immune problems or anaphylactic reactions and had no direct effect on nerves or vessels (Badalamente and Hurst 1996). Furthermore, collagenase manufactured by BTC had been approved for use during burn wound debridement in patients in the USA by the FDA. This prior

human use of collagenase was an important step forward. If a new component (drug) has not been previously approved for human use by the FDA, then three different species toxicology studies have to be done before any human studies to verify its safety. Animal toxicology testing is very expensive. Because collagenase had already been used in human burn wound treatment, further animal toxicology studies were not required by the FDA. Therefore, it seemed like a natural progression to test collagenase in Dupuytren Disease.

The initial investigations of collagenase in the treatment Dupuytren Disease was complicated by the sudden and unexpected appointment of Dr. Hurst as the acting Professor and Chairman of the Orthopedic Department. The early 1990s were a tumultuous time in the Stony Brook Orthopaedic Department's development. Dr. Hurst's research conducted with Dr. Badalamente became just one aspect of a multifaceted job.

To go forth with using collagenase in humans for Dupuytren Disease, an investigational new drug (IND) number was needed from the US Food and Drug Administration. This bureaucratic regulatory process was done by Drs. Hurst and Badalamente, and ultimately an IND was obtained by SUNY Stony Brook from the FDA in 1994. This allowed clinical trials of collagenase with Stony Brook as the sponsor to begin. Orphan Drug Status was also given to Stony Brook by the FDA later in 1997 which provided grants for the research and 7 years of patent exclusivity to the use of collagenase if it could be approved by the FDA and successfully commercialized for Dupuytren Disease.

## 14.3 Preclinical Lab Work: Systemic Toxicology Studies and Biomechanical Studies

The first investigation involved studying the Dupuytren cords that were removed from patients undergoing surgical fasciectomy. The cords were brought to the lab, injected with various dose units of collagenase, incubated overnight at body temperature, and then pulled to failure (rupture) with a materials testing machine (Starkweather et al. 1996). The results of this study were very promising. It was discovered that the force needed to pull apart the Dupuytren cords was actually less than the force produced during normal finger extension from a closed fist position. This in vitro biomechanical study showed that clostridial collagenase injected into Dupuytren cords obtained from surgical resection could significantly reduce tensile modulus of the cord tissue and allow the cord to break apart easily.

The initial biomechanical testing was expanded by testing more surgical specimens. Early observation using Dupuytren cords treated with 600 units of collagenase revealed a 93 % reduction in tensile modulus compared with control tissue (2.16 Mpa versus 33.02 Mpa). In 3 treated cords, complete disruption of the specimen occurred during tensile testing. In additional studies, 20 Dupuytren cords were surgically removed from patients and randomly assigned to treatment with collagenase (150 units, 300 units, or 600 units) or control buffer. Mechanical testing of tensile modulus was performed 24 h after treatment during which cords were placed under a constant displacement of 9 mm/s until cord rupture (Badalamente and Hurst 1996).

These studies showed a clear inverse relationship between collagenase dose and the force needed to disrupt Dupuytren cords. Comparison of these data with previous reports of the average muscle tendon extensor force of each finger suggested that 300 units collagenase was the minimum effective dose sufficient to cause cord rupture by the normal extensor forces of the index, long, ring, and small fingers. Furthermore, histological examination of collagenase-treated cords revealed collagen lysis, which was increasingly apparent with incremental doses of collagenase (Starkweather et al. 1996; Hurst et al. 1996).

Although these results were promising, the FDA still did not immediately approve the testing of collagenase in humans with Dupuytren Disease. The FDA was concerned collagenase might damage the neurovascular structures in the human palm and fingers. Therefore, an additional study was performed utilizing a rat tail

model. The rat tail has nerves, arteries, veins, small bones, and a tendon. Thus, it was the perfect animal model for a finger. This preclinical in vivo lab safety study showed that collagenase could be safely injected into the tendon of a rat tail without damaging the neurovascular structures, or bones. The injected tendon was disrupted by the collagenase, but the other collagen-containing structures remained intact and the rats' tails remained viable (Badalamente and Hurst 1996).

In this model, the right sacrocaudalis ventralis lateralis (tail) tendon was exposed in adult male rats and injected with purified clostridial collagenase (150 units in 10 μL neutral buffer or 300 units in 10 μL buffer, $n = 7$ per group) or a control solution (10 μL of sterile distilled water; $n = 7$).

Tissue prepared from control animals showed intact collagen bundles and adjacent skin and minimal evidence of collagen microtears. Injection-site sections prepared from animals euthanized at 1 h after injection with 150 units clostridial collagenase revealed minimal collagen lysis within the tendon, with damage evident in some collagen bundles but not in others. In the animals euthanized 24 h after injection of 150 units clostridial collagenase, more extensive collagen lysis was present, with clear evidence of collagen lysis with collagen bundle discontinuity. Similarly, in animals treated with 300 units clostridial collagenase, collagen lysis was evident at both 1 and 24 h following injection, although lysis was considered more extensive at the latter time point. Clearly, collagenase's effect increased during the 24 h time period.

Some tail tendon lysis occurred in all animals receiving 150 or 300 units clostridial collagenase, no extravasation of collagenase to adjacent tissues was noted, and no microhemorrhage other than that associated with the surgical procedure was present. All adjacent structures, including ventral artery and vein, nerve bundles, muscle, and skin, remained intact and showed normal anatomy. In all cases, the sections prepared from tissue proximal and distal to the injection site also showed normal anatomy. After this study was successfully completed, the FDA then approved collagenase for trial experiments in human patients.

## 14.4 FDA-Regulated Clinical Phase 1 and 2 Trials Begin

The first study done in human patients was done in 1995 and utilized only 1/20 of the dose that is currently used today. So needless to say, none of the patients ($n = 6$) that were treated with this dose experienced any clinical benefit. Clearly, living Dupuytren cords in patient hands were not disrupted by this small injection of collagenase that had disrupted Dupuytren cords in the laboratory studies. Drs. Hurst and Badalamente were disheartened but decided that larger doses should be tried. The FDA then approved a dose escalation study. In this study design, the amount of collagenase given was increased using a dose-doubling scheme. In this type of study, the dose is doubled until a therapeutic effect is achieved or until adverse events suggest toxicity. If therapeutic success cannot be achieved without toxicity, the study has to be discontinued. Ideally, therapeutic success is achieved by doubling the dose before toxicity is encountered. Using this dosing scheme, 1 out of 7 patients experienced a Dupuytren cord rupture, leading Drs. Hurst and Badalamente to believe that collagenase could potentially be used to treat Dupuytren contracture (Badalamente and Hurst 2000).

The next steps were the phase 2 trials followed by two 3 phase trials to examine the efficacy and safety of clostridial collagenase injections with Dupuytren contracture.

The initial *pilot study* using the results of the in vivo biomechanical study as a basis, an open-label, dose escalation, phase 2, pilot study evaluated 35 patients (32 men and 3 women) with a mean age of 65 years. The primary efficacy end point was correction of deformity to within 0–5° of normal (0°) within 30 days of the last injection. The first 6 patients, as previously described, were treated in the dose escalation phase of the protocol and received single injections of 300, 600, 1200, 2400, 4800, or 9600 units of collagenase. No clinical benefit was observed in these

patients. The remaining 29 patients received injections of 10,000 units (0.58 mg) collagenase. Up to 6 repeat injections were given 4–6 weeks apart if the joint angle did not correct to within 0–5° of normal. The mean degree of initial joint contracture was 42° ± 13° for MP joints and 52° ± 16° for PIP joints. Thirty of 34 MP joints (88 %) and 4 of 9 PIP joints (44 %) treated with 10,000 units of collagenase were fully corrected or improved to within 5° of normal. Repeat injections were required in 15 patients. Overall, recurrence occurred in 3 MP joints 2 years post injection and 1 PIP joint 3 months post injection (Badalamente et al. 2002).

*Study 101* A single-center, randomized, placebo-controlled, double-blind, phase 2a study was subsequently conducted in 49 patients (42 men and 7 women), 36 patients with MP joint contracture, and 13 patients with PIP joint contracture. The mean age of patients was 65 years. The primary efficacy end point was correction of deformity to within 0–5° of normal extension (0°) within 30 days of the last injection. Patients not meeting the primary end point after one injection in the double-blind study could receive up to 4 additional injections of 10,000 units (0.58 mg) of collagenase on an optional, open-label basis. The open-label extension was available to all patients, including those randomized to receive placebo during the double-blind phase. In the double-blind study, MP and PIP joints were randomized to receive 10,000 units of collagenase ($n = 18$ and $n = 7$, respectively) or placebo ($n = 18$ and $n = 6$, respectively). The mean baseline contracture of joints before collagenase injections was 44° ± 17.4° for MP joints and 53° ± 18.7° for PIP joints. Overall, more joints with cords treated with collagenase than placebo achieved correction of deformity to within 0–5° of normal and within a shorter time. One month after injection with collagenase, 14 of 18 MP joints (78 %) showed correction of contracture to within 0–5° of normal compared to 2 of 18 MP joints (11 %) after injection with placebo. The 4 patients who did not achieve correction of deformity to within 0–5° of normal with the first injection were treated again, and all showed correction of contracture to within 0–5° of normal 1 month after the second injection. Of the patients with PIP joint contractures, 5 out of 7 (71 %) treated with collagenase and none treated with placebo were corrected to 0–5° of normal 1 month post injection. Flexion and grip strength did not significantly change compared with baseline values in either the MP- or PIP-treated or placebo groups. Recurrence occurred in 4 MP joints and 4 PIP joints in mean follow-up periods of 4 years and 3.8 years, respectively. Further follow-up at 5 years showed recurrence in only one additional MP joint (Badalamente et al. 2002).

Then in 2001 the FDA intervened again and proposed the question "are you using the minimal effective dose to achieve the desired outcome?" To answer this question, an additional, multicenter phase 2 study was designed, in cooperation with our colleague Dr. VR Hentz at Stanford University. Eighty patients (64 men and 16 women) with a mean age of 63.9 years took part in a randomized, double-blind, placebo-controlled, dose-response, phase 2b trial conducted at 2 test centers. The objective was to determine again if, indeed, 10,000 units (0.58 mg) was the minimum safe and effective dose. Fifty-five patients had MP joint contractures (mean baseline contracture of 50° ± 4.9°) and 25 had PIP joint contractures (mean initial contracture of 49° ± 9.8°). Joints were randomized to receive a single injection of 2500 (0.145 mg), 5000 (0.29 mg), or 10,000 (0.58 mg) units collagenase or placebo.

A comparison of dose groups showed that in both MP and PIP joints, the return to normal extension (0–5°) was higher in patients who received 10,000 units of collagenase 1 month after injection compared with the lower collagenase doses or placebo. Eighteen of 23 patients (78 %) who received 10,000 units of collagenase responded to normal extension by 1 month compared to 10 of 22 patients (45 %) who received 5000 units and 9 of 18 (50 %) of patients who received 2500 units. No response was observed in the placebo group. An open-label extension of this study permitted up to 4 additional 10,000-unit collagenase injections. Overall, 59 % (22 out

of 37) achieved 0–5° with retreatment; success was higher in MP joints (66.6%) than PIP joints (46.2%). Recurrence occurred in 1 MP joint and 1 PIP joint after mean follow-up periods of 2 years and 12.5 months, respectively. Further follow-up at 5 years indicated recurrences in 5 (of 37) MP joints and 4 (of 20) PIP joints.

*Safety in Phase 2 Studies* In all 3 phase 2 studies, collagenase injections were well tolerated. Some minor, transient adverse events, such as injection site tenderness, hand ecchymosis, and edema, were reported, but all resolved within 6–7 weeks (mean time to resolution of 1–2 weeks) of the injection. Collagenase injection did not induce an adverse systemic immune reaction, even after repeated administration. Although some patients had detectable serum IgE titers following collagenase injection, no induced allergic reactions were reported (Badalamente and Hurst 2007).

*Summary of Phase 2 Studies* Data from the phase 2 studies showed that clostridial collagenase injection provides superior clinical success rates compared with placebo injections and has merit as a nonsurgical treatment for patients with Dupuytren contracture. After these studies were performed, the FDA team overseeing the clinical trials then changed. This new team had approved Vioxx which was later taken off the market. Needless to say, this team was very cautious about approving any other drugs, including collagenase.

## 14.5 Commercialization and Manufacturing Woes

Next, the issues related to commercialization and manufacturing threatened to derail the development of collagenase for Dupuytren contracture treatment. Phase 3 trials can be extremely expensive, and, therefore, BTC sold their licensing technology to Auxilium Pharmaceuticals, and the IND, which was held by the University at Stony Brook, was transferred to Auxilium in 2005. Pfizer also got permission to market collagenase in Europe as Xiapex in 2008. A revised US Patent was then reissued and granted in 2007 to BTC.

It was at this point that Dr. Hurst and Dr. Badalamente thought everything was going well and collagenase would finally be fully approved after phase 3 trials. However, the FDA also looks at manufacturing of each new drug. Since BTC was manufacturing collagenase in a small factory in Puerto Rico, the FDA said it was out of date because it was over 30 years old. The FDA would not approve any drugs manufactured from this old factory and required that a new manufacturing facility be built. Thus, the next challenge was to build a new factory. Fortunately, Auxilium was able to build the new factory and finally started to produce the drug. Finally, collagenase acceptable to the FDA was available and Phase 3 trials could begin.

## 14.6 FDA-Regulated Clinical Phase 3 Trials Begin

*Study 303* Based on the promising data from phase 2 investigations, the efficacy and safety of clostridial collagenase were assessed in a phase 3 randomized, double-blind, placebo-controlled clinical trial at Stony Brook Medical Center. This trial included 35 patients with Dupuytren contracture who were randomized in a 2:1 ratio to receive injections of collagenase ($n=23$; 10,000 units (0.58 mg) or placebo ($n=12$). In total, 21 patients had affected MP joints, and 14 had affected PIP joints: mean baseline joint contracture was 51° for MP joints and 46° for PIP joints. Primary and, when possible, secondary and tertiary joints were identified for each patient, resulting in a total of 55 affected joints. Patients could receive up to 3 injections in the primary joint at 4- to 6-week intervals. Those who achieved correction to 0–5° of normal after the first injection were eligible to be re-randomized to further treatment for a secondary or tertiary joint. All patients wore splints at night for 4 months after injection. The primary efficacy end point was a reduction in deformity in the primary joint to within 0–5° 30 days after the last injection. Additional end points included time to clini-

cal success, number of injections required to achieve correction to 0–5° of normal, and recurrence (defined return of contracture to ≥20° in successfully treated joints).

Of the 35 randomized patients, 33 completed the double-blind study. In addition, 9 patients were re-randomized after successful treatment of the primary joint: 6 received collagenase and 3 received placebo. One tertiary joint was also treated with collagenase. Overall, 21 of 23 (91 %) patients who received collagenase and 0 of 12 (0 %) who received placebo for a primary joint achieved 0–5° of normal ($P < .001$). Both joint types responded well to collagenase treatment with correction to 0–5° of normal attained in 12 of 14 (86 %) MP joints and 9 of 9 (100 %) PIP joints. Furthermore, 16 of 23 patients achieved correction to 0–5° of normal with a single collagenase injection, whereas 2 patients required 2 injections and 3 patients required 3 injections. Overall, the mean number of injections for correction to 0–5° of normal was 1.4, and median time to clinical success was 8 days. Correction to 0–5° of normal was also achieved in 5 of 6 (83 %) collagenase-treated secondary joints and in the only collagenase-treated tertiary joint.

*Study 404* Patients in the double-blind study 303 who failed to achieve correction to 0–5° of normal, or who had other involved joints of the same or contralateral hand, were eligible to continue treatment in the open-label extension study (study 404). During this study, patients could receive up to 3 injections of collagenase (10,000 units) in a single joint, with no more than a total of 5 injections across both double-blind and open-label studies. Nineteen patients with 35 involved joints were included in the open-label study, including 15 patients who received placebo to either primary or secondary joints in the double-blind phase and 4 patients who failed to achieve clinical success while receiving collagenase during the double-blind study. Clinical end points in the open-label study were the same as those used in the double-blind study. In total, 17 (89.5 %) of 19 patients achieved correction to 0–5° of normal in at least 1 treated joint. Similar rates of correction to 0–5° of normal were achieved in MP and PIP joints. In total 27 of 35 (77 %) affected joints were successfully treated, including 14 of 16 (88 %) MP joints and 13 of 19 (68 %) PIP joints. Importantly, 23 affected joints were successfully treated with a single injection, with response rates similar in MP and PIP joints. The mean number injections required to achieve correction to 0–5° of normal was 1.5 for MP joints and 1.3 for PIP joints. In total, throughout the double-blind and open-label studies, a total of 62 affected joints were treated, of which correction to 0–5° of normal was achieved in 54 (87 %). All patients were subsequently followed for 12 months, and 27 of 54 joints were followed for 2 years. During this period, 4 PIP joints and 1 MP joint showed recurrence of contracture. For the PIP joints, recurrence was 20° and 30° at 12 months and 40° at 24 months.

### 14.6.1 Safety/Adverse Events

In general, collagenase therapy was well tolerated in phase 2 and phase 3 clinical studies, with all adverse events graded as mild to moderate and most resolving within about 1–3 weeks. Injection-site pain, hand ecchymosis, and edema occurred but resolved with mean times to resolution of 1–2 weeks. Lymphadenopathy (usually axillary or elbow) was also observed in a minority of patients (approximately one third) in both phase 2 and phase 3 studies.

There were 11 skin lacerations at cord rupture in the phase 3 studies. These lacerations occurred primarily in patients who had experienced severe baseline (>80°) contracture over many years. All lacerations were effectively healed through secondary intent without surgery and did not affect clinical outcome. Finally, no systemic immunological adverse events were reported.

Next, Auxilium sponsored and started the CORD (Collagenase Option for Reduction of Dupuytren) studies. This was a massive undertaking with 16 sites in the USA participating as well as 5 sites in Australia. This phase 3 trial would be a final data source for the new drug application that would be submitted to the FDA

for collagenase treatment of Dupuytren Disease. However, just before this study was about to begin, it was noticed that some of the bottles containing the lyophilized collagenase (Xiaflex) did not have the usual size "cake" of lyophilized drug. Some of the cakes were smaller than usual, and the bottles had a milky-looking stain on the inside of the glass bottle containing the drug. Although the medication still worked, it didn't look right. The FDA immediately put the final phase 3 trial on hold. It took nine months to sort out that a little moisture was leaking into the bottles during manufacturing, and some of the collagenase protein was partially dissolved and caused this milk glass appearance instead of the normal full-sized "cake" appearance. Once the moisture leakage was identified, new tighter rubber caps were designed for the bottles containing the lyophilized Xiaflex, and the "cake" all remained intact. Once the FDA approved this manufacturing change, the CORD studies were started. The study showed that 64 % of the MP joints were able to be fully extended after treatment.

*CORD I and CORD II* In these studies (Hurst et al. 2009), patients were required to have a minimum 20° of contracture and were randomized using a ratio of 2:1 to receive collagenase (0.58 mg) or placebo. The primary objective of CORD 1 and CORD 2 is normalization of the joint to within 0–5° of normal (0°) after up to 3 injections of study treatment. Upon completion of a double-blind phase, patients who initially received placebo or who have other affected joints were eligible for enrollment in open-label extension phases, during which, all patients will receive collagenase treatment.

Importantly, a statistically significant difference was observed in the ability of clostridial collagenase to meet the primary endpoint—correction to 0° to 5° of normal after the last injection—compared with placebo. Overall, 64 % of joints treated with collagenase vs. 6.8 % treated with placebo ($P < .001$) were corrected to 0–5° of normal after the last injection in CORD I. In CORD 2, the rates were 44.4 % vs. 4.8 % ($P < .001$). The most common adverse events reported in CORD I and II were pain, swelling, bruising, and pruritus at the injection site. No systemic allergic reactions were reported. Overall, 7 serious adverse events possibly related to collagenase were reported, including 2 confirmed tendon ruptures, 1 pulley ligament injury, and 1 complex regional pain syndrome.

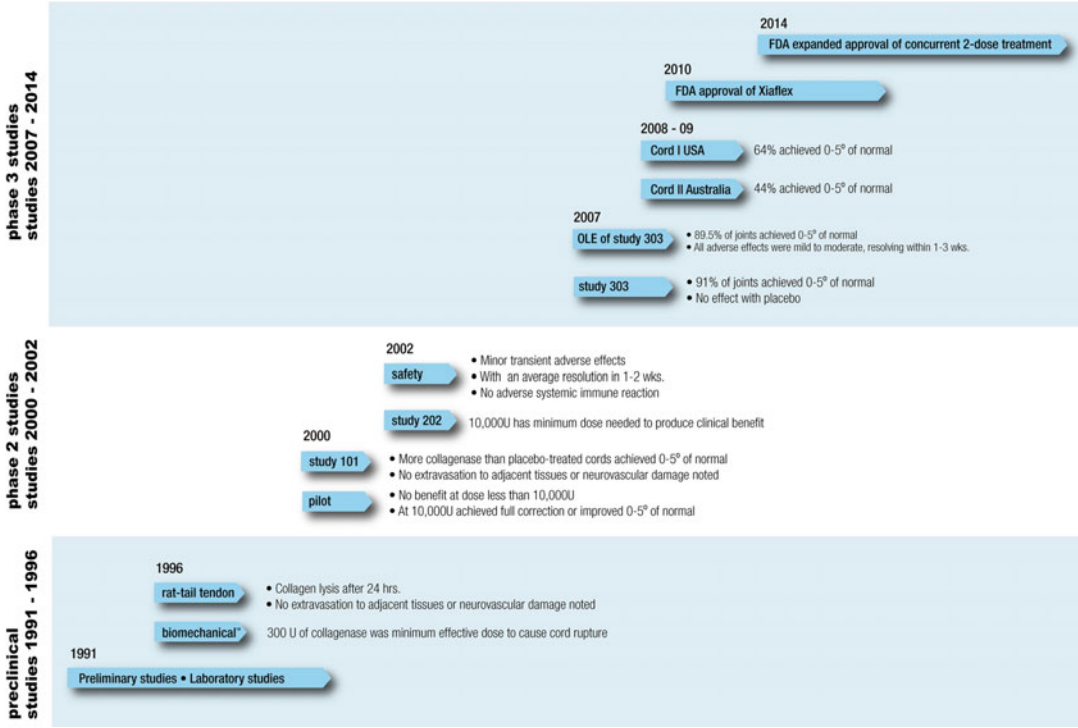
The CORD study was published in *The New England Journal of Medicine* in 2009, *Injectable Collagenase Clostridium Histolyticum for Dupuytren Contracture* (Hurst et al. 2009).

In September of 2009, the FDA convened an Advisory Committee to look at all the data from all collagenase studies and the Advisory Committee stated that they would recommend that Xiaflex be approved for use in humans. The committee vote was 12-0 in favor of approval. Finally, in February of 2010, the US FDA approved Xiaflex. In 2010, there were only six biologic compounds to be approved by the FDA to become drugs. Dr. Hurst, Dr. Badalamente, and Dr. Wang (for a separate adhesive capsulitis study) were given the honor of the Orthopaedic Research and Education Foundation and American Academy of Orthopaedic Surgeons Clinical Research Award. There is only one of these awards given per year in the USA. A symposium was then held in April of 2010 in Stony Brook focused on Dupuytren Disease and treatment with Xiaflex. A DVD of this symposium was donated to the American Society for Surgery of the Hand for distribution as an educational resource (Hurst and Badalamente 2010).

## 14.7 Summary of Studies in Dupuytren Contracture (Table 14.1)

Injectable clostridial collagenase is a promising treatment for patients with Dupuytren contracture. Dose-ranging, phase 2 clinical trials identified an optimal collagenase dose of 10,000 units (0.58 mg), balancing excellent clinical efficacy outcomes with a favorable tolerability profile. High rates of correction of joint contracture to 0–5° of normal after the last injection were

**Table 14.1** Timeline for the development of injectable collagenase *Clostridium histolyticum* for the treatment of Dupuytren Disease




attained in both MP and PIP joints and in patients of all ages, as demonstrated in the phase 3 studies. Encouragingly, clinical efficacy appears to be reasonable with long-term follow-up of patients from the first phase 3 clinical trial. Adverse events are typically local reactions to the injection, are mild to moderate in severity, and dissipate within 1–3 weeks of injection. No serious or systemic immunological adverse events have occurred.

## 14.8 Insurance Approval

In February 2010, Xiaflex was approved by the FDA; however, insurance companies in the USA still considered it experimental and were not routinely covering the treatment of Dupuytren contracture with Xiaflex. Finally, in the summer and fall of 2010, medical insurance coverage for Xiaflex became available for most patients. Once this payment bearer was overcome, there were 852 patients on the waiting list at the University Hand Center at Stony Brook who were requesting treatment for their Dupuytren contractures with Xiaflex. It took two years to treat the backlog of 852 patients.

In January 2011 the public media became involved in the Dupuytren Disease and the Xiaflex story. Xiaflex was used in the TV show "Royal Pains," where a concierge physician in the episode called "Muligan" injected a Xiaflex to his friend's hands over lunch and manipulated his fingers during the golf outing the next day. Obviously this was a TV dramatization which took considerable literary license with the FDA's labeling recommendations. However, this single TV show did increase the US public's awareness of Dupuytren Disease and Xiaflex treatment.

After Xiaflex became available for clinical use in the USA, other international pharmaceutical companies made partnership arrangements with Auxilium. These included Pfizer in 2008 and SOBI in 2014 to provide Xiapex (Xiaflex's European

name) in the European Union, Actelion provided it in Canada and Australia in 2011, Asahi Kasei Pharmaceutical Corporation in Japan in 2012 with release in 2016, and lastly Auxilium which was bought by Endo Pharmaceuticals in 2015.

Xiaflex (Xiapex in Europe) is recommended for patients with a palpable cord causing MP joint contractures of 20–30° or more as well as PIP joint contractures of 20° or more that are getting progressively worse over time and a positive tabletop test. For the actual injection of Xiaflex, Dr. Hurst prefers to use a 1 mL hubless syringe with a fixed 27 gauge needle. 0.25 mL is injected for the MP joint and 0.20 mL for the PIP joint; each injection contains 0.58 mg of collagenase (Xiaflex). Aliquots of the 0.58 mg dose are placed in 3–5 separate locations in the Dupuytren cord. For the manipulations, approximately 9 cc of 1 % lidocaine is used with 1 cc of bicarbonate buffer to give a per manipulation local field block. The finger manipulation or finger extension procedure is always done in a four-step manner: (1) extend the MP joint with PIP flexed, (2) extend the PIP joint with the MP flexed, (3) extend the MP and PIP joints simultaneously, and (4) with the MP and PIP extended, push on any areas with residual cord with the surgeon's opposite thumb or index finger. During the manipulation, it is important to be as gentle as possible to avoid skin tears. Skin tears often start through areas of skin with blood blisters so extra caution is warranted when blisters are present after injection.

## 14.9 The Future of Xiaflex in Dupuytren Disease

The use of Xiaflex is currently approved for use in MP and PIP joints; however, Dr. Hurst has successfully used it in DIP joints and thumb contractures and first web contractures as well. Although these treatments are "off-label" uses of Xiaflex, Xiaflex has proved to be beneficial in Dr. Hurst's patients for DIP flexion contractures, web contractures, and thumb contractures. Xiaflex has also been used successfully in the treatment of cord combinations such as the "Y" cord which is a combination of a central cord and a natatory cord. By dividing a single Xiaflex dose and by using two concurrent doses in the same hand, which has now been FDA approved, multiple complex cord combinations can now be treated in a single sitting. Recent studies have also allowed the FDA labeling to include delayed finger extension timings at 48 and 72 h after injection. Concurrent double-dose treatment has proven to be both efficacious and safe to administer for contractures of two joints in the same finger or for fixed MP or PIP flexion contractures in different fingers in the same hand (Gaston et al. 2015).

A study was performed where patients with 2 or more contractures in the same hand caused by palpable cords participated in a 60-day, multicenter, open-label, phase 3b study. Two 0.58 mg CCH doses were injected into 1 or 2 cords in the same hand (1 injection per affected joint) during the same visit (Gaston et al. 2015). Finger extension was performed approximately 24, 48, or 72 or more hours later. Changes in FFC (fixed flexion contracture) and range of motion, incidence of clinical success (FFC $\leq 5°$), and adverse events (AEs) were summarized. The study enrolled 715 patients (725 treated joint pairs), and 714 patients (724 joint pairs) were analyzed for efficacy. At day 31, mean total FFC (sum of 2 treated joints) decreased 74 %, from 98° to 27°. Mean total range of motion increased from 90° to 156°. The incidence of clinical success was 65 % in metacarpophalangeal joints and 29 % in proximal interphalangeal joints. Most treatment-related AEs were mild to moderate, resolving without intervention; the most common were swelling of treated extremity, contusion, and pain in extremity. The incidence of skin lacerations was 22 % (160 of 715). Efficacy and safety were similar regardless of time to finger extension.

Therefore, collagenase *Clostridium histolyticum* (Xiaflex) can be used to effectively treat 2 affected joints concurrently without a greater risk of AEs than treatment of a single joint, with the exception of a small increased skin tear rate. The incidence of clinical success in this study after 1 injection per joint was comparable to phase 3 study results after 3 or more injections per joint. There is no greater risk of adverse events than treatment of a single joint, with the exception of

skin laceration. Two concurrent CCH injections may allow more rapid overall treatment of multiple affected joints, and the ability to vary the time between CCH injection and the manipulation may allow physicians and patients' greater flexibility with scheduling treatment. Manipulations have been performed successfully up to 48 and 96 h after injection of Xiaflex.

In conclusion, Xiaflex/Xiapex is an excellent and useful alternative to surgery for patients with advanced Dupuytren Disease. However, whether a Xiaflex injection or surgery is performed, the Dupuytren cord can still recur. The success in treating patients with Dupuytren contracture comes from experience in making a decision with your patient as to the best treatment option for the best outcome possible. The surgeon and patient must always understand that Dupuytren Disease cannot truly be cured but only managed and that recurrence is always a possibility.

**Conflict of Interest Statement** Lawrence C. Hurst and Marie Badalamente of Partial Xiaflex/Xiapex royalty from BioSpecifics Technologies Corp. Marie Relevo and Kerri Kulovitz have nothing to declare.

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