COLLAGENASE CLOSTRIDIUM HISTOLYTICUM (XIAFLEX) DEVELOPMENT

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SUMMARY
Fibroproliferative disorders can affect the musculoskeletal system and often limit joint range of motion, seriously impacting quality of life. The fixed-flexion deformity of Dupuytren's contracture and adhesive capsulitis (frozen shoulder) are 2 such disorders. A debilitating deformity of the metacarpophalangeal and proximal interphalangeal joints of the hand, Dupuytren's contracture is characterized by a progressive accumulation of collagen that causes Dupuytren's cords to form, leading to a progressive flexion of the fingers. The standard of care is surgical fasciectomy, which in many cases has suboptimal treatment outcomes and a high recurrence rate. Injectable Clostridial collagenase represents a novel, investigational nonsurgical approach to the treatment of Dupuytren's contracture. Early, proof-of-principle, basic science studies, using a rat tail tendon model and surgically removed Dupuytren's cords, yielded favorable results. Clinical studies in humans were then conducted, where the primary end point was reduction in contracture to within 0° to 5° of normal extension (0°) after the last injection. Phase 2 studies (Dupy-101 and Dupy-202), which confirmed the optimal dose of collagenase as 10,000 units (0.58 mg), showed injectable Clostridial collagenase reduced contractures in metacarpophalangeal and proximal interphalangeal joints to within 0° to 5° of normal after the last injection in a substantial number of joints and was well tolerated. Clinical efficacy results from phase 3 studies (Dupy-303, Dupy-404, CORD I, and CORD II) confirmed the efficacy and safety of injectable Clostridial collagenase as a viable nonsurgical intervention for the treatment of patients with Dupuytren's disease, translating the observations made in the laboratory into the clinical setting. An additional study in humans with adhesive capsulitis has also yielded promising results. Thus, this investigational minimally invasive injection therapy shows potential for patients with fibroproliferative disorders affecting the musculoskeletal system.

Keywords: Dupuytren's contracture, myofibroblasts, injectable Clostridial collagenase, Xiaflex

INTRODUCTION

FIBROTIC TISSUE DISORDERS

Fibrotic tissue disorders, which are characterized by excessive collagen deposits, represent a collection of painful joint conditions that can limit movement, reduce range of motion, and have a negative impact on quality of life. Unfortunately, the specific mechanisms that contribute to the underlying pathophysiology are, in many cases, poorly understood. Two such fibrotic tissue disorders are Dupuytren's disease and adhesive capsulitis (frozen shoulder). Both conditions can result in impaired function, yet treatment options are limited and clinical outcomes are often suboptimal. This document summarizes a large body of preclinical and clinical research conducted to evaluate the feasibility of using injectable Clostridial collagenase as a treatment for fibrotic tissue disorders, primarily Dupuytren's contracture. Additional research on adhesive capsulitis is also presented.

DUPUYTREN'S DISEASE

Dupuytren's disease is a progressive disorder of pathologic collagen deposition characterized by nodules and cords in the palm and fingers. These pathologic changes cause pitting of the overlying cutis and flexion contractures of the fingers, which can be both annoying and frequently disabling.[1]

Myofibroblasts are considered key pathologic cells in the development of Dupuytren's disease. Four- to 20-fold increases in myofibroblast density have been reported in the palmar fascia of patients with Dupuytren's disease. Myofibroblasts facilitate increased collagen production, particularly type-III collagen in the early stages of the disease, which is virtually absent in normal adult palmar fascia [2,3]. Proliferating myofibroblasts synthesize and contract collagen in lines of stress, encouraging further mechanistic changes consistent with the progressive nature of this disease [4]. In the early stages of Dupuytren's disease, changes are manifested as nodules within the palm. As the condition progresses, diseased "cords" cause fingers to progressively flex at the metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints, resulting in well-described fixed-flexion deformity of the hand [5].

The global prevalence of Dupuytren's contracture among Caucasians is estimated at 3% to 6% [4,6,7], and certain patient groups have been identified in which the incidence of Dupuytren's contracture is substantially higher than others. For example, the incidence is at least 7-fold higher in men than in women [4,6], and a strong association exists between onset of Dupuytren's contracture and age. Most patients are older than 50 years at presentation [8]. Further, among patients with diabetes, the incidence of Dupuytren's disease has been estimated at 10.5% [8], although other reports suggest the incidence may be much higher [9,10]. In patients with thyroid disease, incidence rates for Dupuytren's disease of 8.8% have been reported [11].

The standard of care for Dupuytren's contracture is surgery. Fasciectomy is most often the technique of choice [5]. However, surgery is far from ideal as most patients with Dupuytren's disease are elderly or have other significant comorbidities such as diabetes, and as such, do not represent ideal candidates for invasive procedures. In addition, neurovascular injury, hematoma, and infection can occur during or following surgery, and in patients with severe contractures digital nerve damage is a risk.

Reflex sympathetic dystrophy and complex regional pain syndrome can also develop after surgery. Recurrence of Dupuytren's contracture after surgery is a moderate risk: an average of 30% of patients experience a recurrence during the 1st and 2nd postoperative years, then an additional 15% experience a recurrence during the 3rd to 5th years, 10% between the 5th and 10th years, and <10% after 10 years [12].

INJECTABLE CLOSTRIDIAL COLLAGENASE

Investigational injectable Clostridial collagenase, followed by postinjection manipulation (extension of the finger to rupture the cord), is a simple office-based procedure that does not require anesthesia [13]. The Clostridial collagenase under investigation is derived from *Clostridium histolyticum* and has well-described collagenolytic properties [13]. The collagenase preparation consists of multiple collagenase subtypes that are not immunologically cross-reactive, have different specificities, and act synergistically. Delivery of the preparation directly into the cord by injection is intended to lyse collagen and subsequently disrupt the contracted cord (Figure 1) [14].

DUPUYTREN'S CONTRACTURE

First, preclinical studies were designed to assess the collagenolytic properties of Clostridial collagenase and assess the potential for adverse extravasation into adjacent collagen-containing tissues [14,15].

ANIMAL STUDY

For this purpose, a rat tail tendon model was developed, in part because of its resemblance of the human finger, as collagenous structures of the tendon are in close proximity to the neurovascular structures and bone. Using 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 20 μL buffer, n = 7 per group) or a control

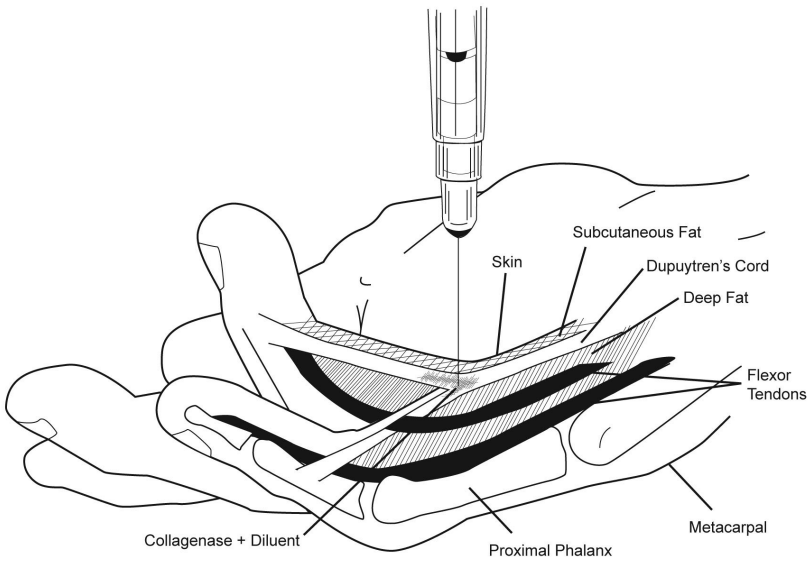

Figure 1. Schematic of Collagenase Injection Procedure.

solution (10 μL of sterile distilled water; n = 7). In each group, 4 animals were euthanized at 1 hour postinjection and 4 animals were euthanized at 24 hours postinjection. A 2-cm portion of each tail (including the injection site) was prepared for sectioning through a process of fixation, decalcification, dehydration, and mounting in paraffin block. Sections were cut, ensuring that both transverse and longitudinal aspects were prepared from each injection-site area. Alternate slides were stained with Masson's trichrome, which renders nuclei stained black; cytoplasm, keratin, and muscle fibers stained red; and collagen stained blue [15].

Tissue prepared from control animals showed intact collagen bundles and adjacent skin and minimal evidence of collagen microtears [15]. Injection-site sections prepared from animals euthanized at 1 hour after injection with 150 units Clostridial collagenase revealed minimal collagen lysis within the tendon, with damage evident in some bundles but not in others. In the animals euthanized 24 hours 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 hour and 24 hours following injection, although lysis was considered more extensive at the latter time point. High magnification examination of samples from the 24-hour time point showed clear evidence of collagen lysis with fibril and bundle discontinuity [15]. Most importantly, 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 [15].

IN VITRO STUDY

An in vitro biomechanical study was next conducted, which showed that Clostridial collagenase injected into Dupuytren's cords obtained from surgical resection could reduce tensile modulus of the cord tissue [14]. Early observation using Dupuytren's cords treated with 3600 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's 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 hours after treatment during which cords were placed under a constant displacement of 9 mm/s until cord rupture [14]. These studies showed a clear inverse relationship between collagenase dose and decreasing stress. 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 [14]. Furthermore, histological examination of collagenase-treated cords revealed collagen lysis, which was increasingly apparent with incremental doses of collagenase [14].

PHASE 2 STUDIES

To date, 3 phase 2 studies have examined the efficacy and safety of Clostridial collagenase injections in more than 160 patients with Dupuytren's contracture [16,17]

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 [16]. The primary efficacy end point was correction of deformity to within 0° to 5° of normal (0°) within 30 days of the last injection. The first 6 patients 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 [16] The remaining 29 patients received injections of 10,000 units (0.58 mg) collagenase. Up to 6 repeat injections were given 4 to 6 weeks apart if the joint angle did not correct to within 0° to 5° of normal. The mean degree of initial joint contracture was 42° ± 13° for MP joints and 52° ± 16° for PIP joints [16]. 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 (Figure 2). Repeat injections were required in 15 patients. Overall, recurrence occurred in 3 MP joints 2 years postinjection and 1 PIP joint 3 months postinjection [16].

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 [17]. The mean age of patients was 65 years and 64.3 years for patients with MP and PIP joint contrac-

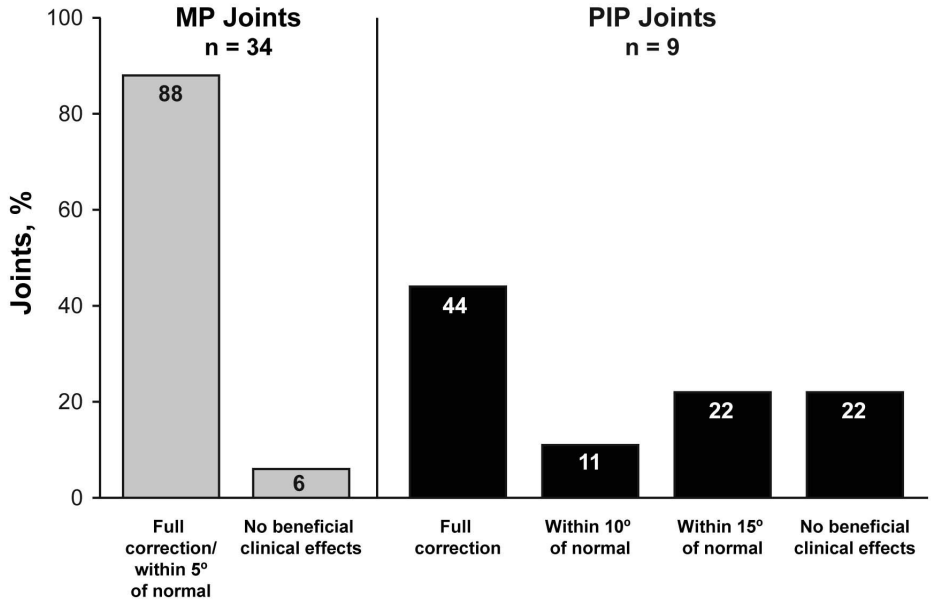

Figure 2. Treatment Outcome in MP and PIP Joints After a Single Collagenase Injection of 10,000 Units in the Dose-Escalation Study.

ture, respectively. The primary efficacy end point was correction of deformity to within 0° to 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 [17].

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 [17]. Overall, more joints with cords treated with collagenase than placebo achieved correction of deformity to within 0° to 5° of normal and within a shorter time (Figure 3). One month after injection with collagenase, 14 of 18 MP joints (78%) showed correction of contracture to within 0° to 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° to 5° of normal with the first injection were treated again, and all showed correction of contracture to within 0° to 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° to 5° of normal 1 month postinjection. Flexion and grip strength did not significantly change compared with baseline values in either the MP or PIP treated

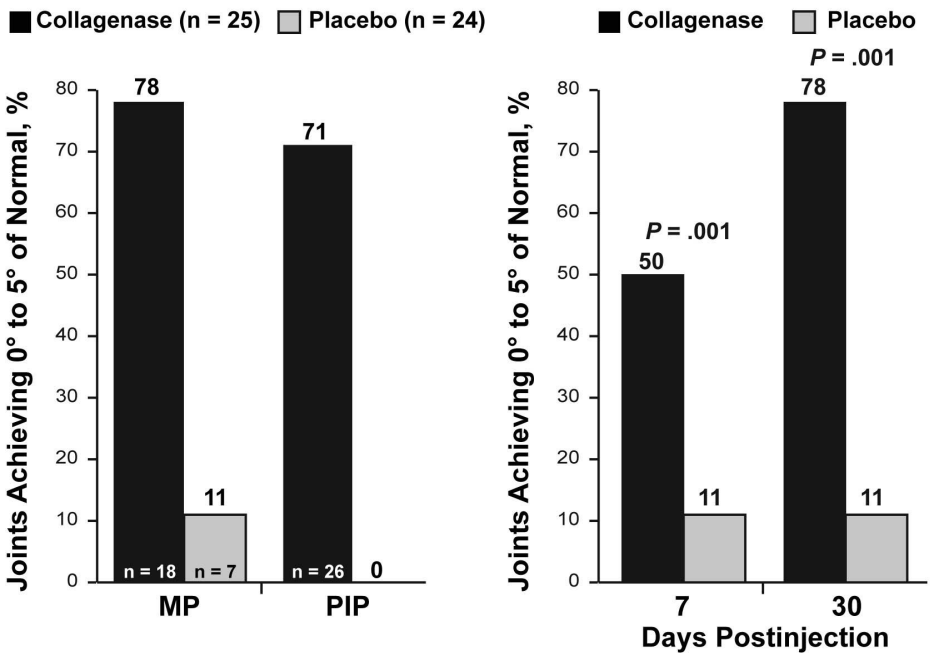

Figure 3. Comparison of Treatment Outcomes in MP and PIP Joints After a Single Injection of Collagenase or Placebo. Achievement of 0º to 5 º of Normal (Left) and Time to Achievement of 0º to 5 º of Normal (Right).

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 [17] Further followup at 5 years showed recurrence in only one additional MP joint.

Study 202. Subsequently, 80 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 [17]. The objective was to determine 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° to 5°) was higher in patients who received 10,000 units of collagenase 1 month after injection compared with the lower collagenase doses or placebo (Figure 4). Eighteen of 23 patients (78%)

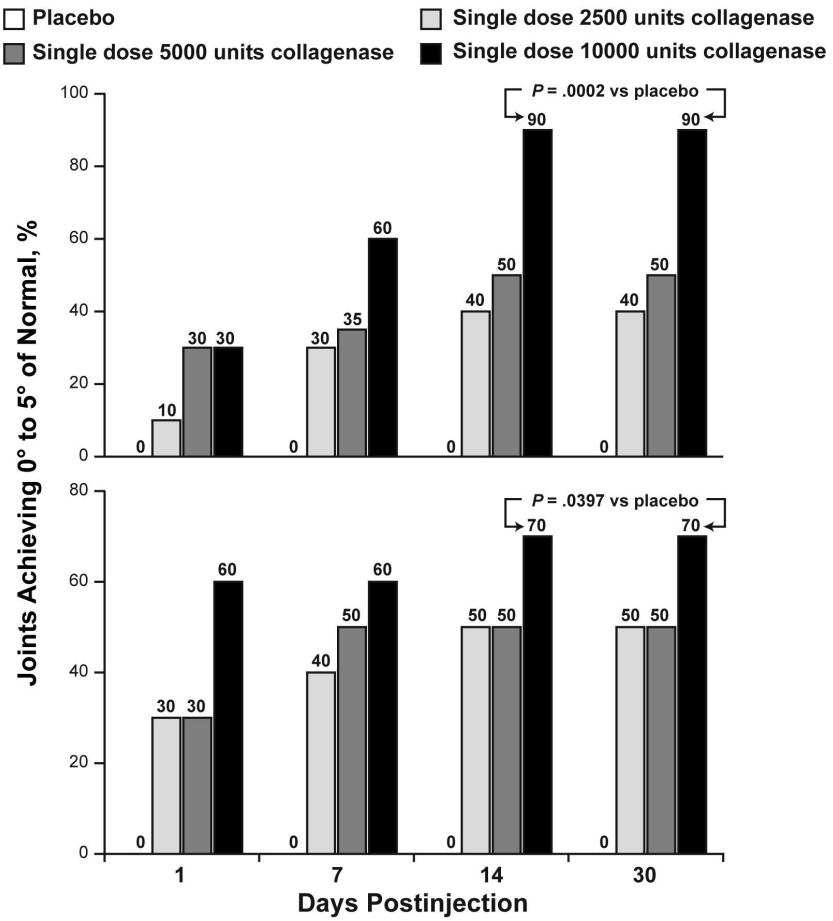

Figure 4. Achievement of 0º to 5º of Normal Stratified by Collagenase Dose and Post-Injection Day for MP (top) and PIP (bottom) Joints.

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 [17].

An open-label extension of this study permitted up to 4 additional 10,000-unit collagenase injections. Overall, 59% (22 out of 37) achieved 0º to 5º 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 [17]. Further followup 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 to 7 weeks (mean time to resolution of 1 to 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.

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's contracture.

PHASE 3 STUDIES

Study 303. Based on the promising data from phase 2 investigations, the efficacy and safety of Clostridial collagenase was assessed in a phase 3 randomized, double-blind, placebo-controlled clinical trial (study 303) [18]. This trial included 35 patients with Dupuytren's 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° to 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° to 5° 30 days after the last injection. [18]. Additional end points included time to clinical success, number of injections required to achieve correction to 0° to 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 [18]. 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° to 5° of normal ($P < .001$; Figure 5). Both joint types responded well to collagenase treatment with correction to 0° to 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° to

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° to 5° of normal was 1.4, and median time to clinical success was 8 days. Correction to 0° to 5° of normal was also achieved in 5 of 6 (83%) collagenase-treated secondary joints and in the only collagenase-treated tertiary joint [18].

Study 404. Patients in the double-blind study 303 who failed to achieve correction to 0° to 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) [18]. 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° to 5° of normal in at least 1 treated joint [18].

Similar rates of correction to 0° to 5° of normal were achieved in MP and PIP joints [18]. 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 (Figure 5). Importantly, 23 affected joints were successfully treated with a single injection, with response rates similar in MP and PIP joints (Figure 5). The mean num-

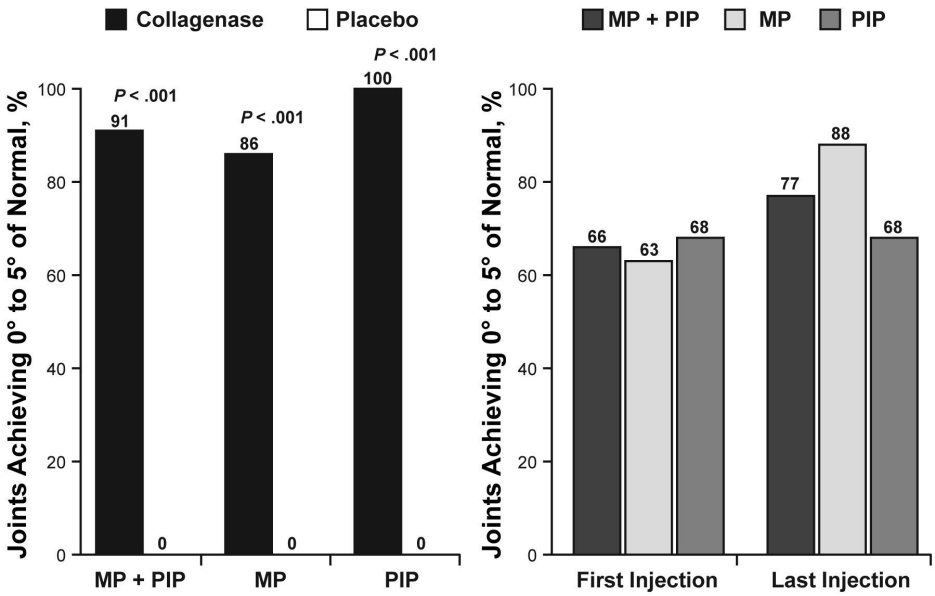

Figure 5. Rates of Achieving 0°-5° of Normal After Multiple Collagenase Injections in Study 303 (Left) and Study 404 (Right).

ber injections required to achieve correction to 0° to 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° to 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 [18].

Case Study. In the phase 3 trial, a 70-year-old man with multiple affected joints and bilateral disease was treated. Dupuytren's contracture was present for 25 (left hand) to 30 (right hand) years. Before treatment, right hand MP and PIP joint contractures were 50º and 35º on the ring finger, respectively, and 20º and 50º on the little finger, respectively (Figure 6, right). Before treatment, left hand MP joint contractures were 35º and 30º on the ring and long fingers, respectively (Figure 6, left). In the double-blind portion of the study, the patient received 3 placebo injections, with no benefit. In the open-label phase of the study, he received 4 single 0.58-mg injections of collagenase (minimum of 4-6 weeks between injections): (1) right, ring, MP; (2) right, little, PIP; (3) left, ring, MP: (4) left, long, MP. Each single injection resulted in a corresponding joint correction of 0° of normal (Figure 6, bottom). At his 3-year follow-up visit, all contractures remained corrected (0º of normal). Adverse events included injection site tenderness or itching and minor skin tears, which required no intervention.

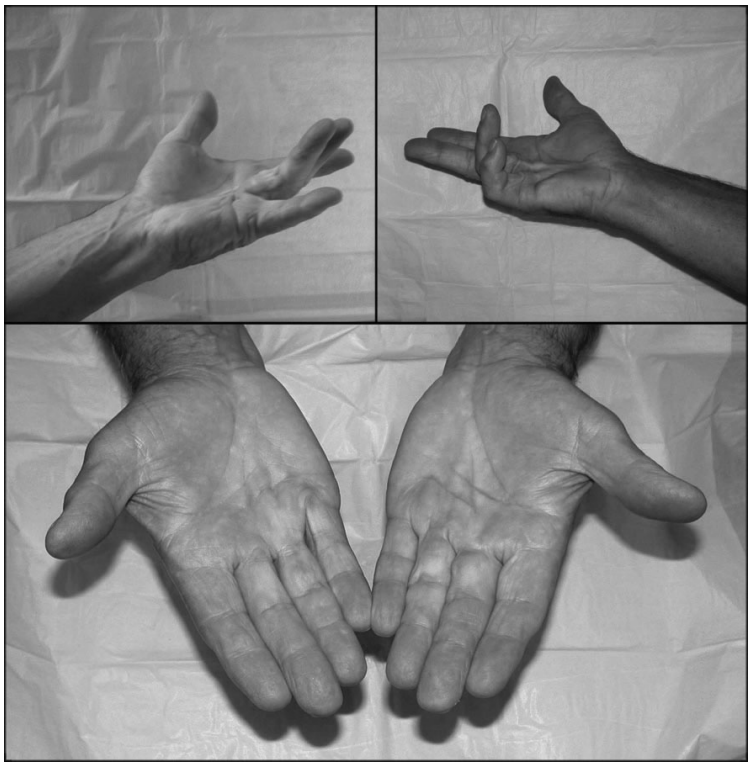

Figure 6. Left hand (left) and right hand (right) before treatment with Clostridial collagenase and both hands after treatment (bottom).

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 to 3 weeks [16-18] Injection-site pain, hand ecchymosis and edema were the most frequently reported adverse events in both double-blind and open-label phase 3 studies, with mean times to resolution of 8 to 15 days and 2 to 9 days, respectively. Lymphadenopathy (usually axilliary 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 (3 in the double-blind study and 8 in the open-label study) and 3 in the phase 2 studies, with none in occurring in placebo patients. These lacerations occurred primarily in patients who had experienced severe baseline (>80°) contracture over many years [17,18]. All lacerations were effectively healed through secondary intent, and did not affect clinical outcome. Finally, no systemic immunological adverse events were reported.

PHASE 3 STUDIES

The clinical development of Clostridial collagenase for the treatment of Dupuytren's contracture was transferred to Auxilium Pharmaceuticals who moved forward with further clinical research. Two additional phase 3 studies, CORD I (Collagenase Option for Reducing Dupuytren's) and CORD II, were conducted concurrently in the United States and Australia, respectively (Table 1). Joint I and II are 2 additional, open-label, phase 3 studies in about 600 patients.

CORD I and CORD II

In these studies, 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° to 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 (Figure 7).

Preliminary data from the double-blind phases of CORD I and CORD II were released (Table 1). (Auxilium press release, June 3, 2008) Importantly, a statistically significant difference was observed in the ability of Clostridial collagenase to meet the primary end point—correction to 0° to 5° of normal after the last injection—

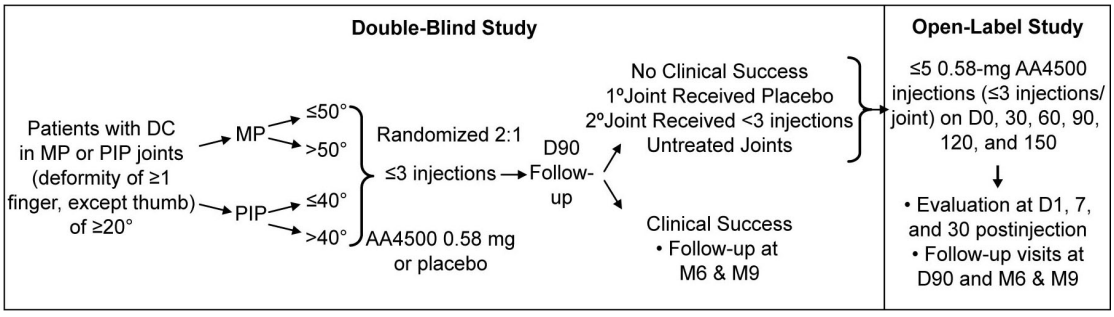

Figure 7. Study Design for CORD I and CORD II studies.

Table 1. Results from the CORD I and CORD II studies.
All data applies to primary joint 30 days after last injection. All comparisons between collagenase and placebo within CORD I and CORD 2 were statistically significant (P <.001)

	CORD I		**CORD II**	
Sites	16 in Unites States		5 in Australia	
MP:PIP joints	2:1		1:1	
	Collagenase	**Placebo**	**Collagenase**	**Placebo**
Evaluable joints, n	203	103	45	21
Joints achieving 0º-5º of normal, % (n/N)	64 (130/203)	6.8 (7/103)	44.4 (20/45)	4.8 (1/21)
Average improvement, % (baseline/after last injection)	79.3 (50.2º/12.2º)	8.6 (19.1º/45.7º)	70.5% (53.2º /16.7º)	13.6 (50.0º /44.3º)
Joints achieving ≥50% reduction in contracture from baseline, % (n/N)	84.7 (172/203)	11.7 (12/103)	77.8 (35/45)	14.3 (3/21)

compared with placebo. Overall, 64% of joints treated with collagenase vs 6.8% treated with placebo (P < .001) were corrected to 0° to 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: 2 confirmed tendon ruptures; 1 pulley ligament injury, 1 complex regional pain syndrome.

SUMMARY OF STUDIES IN DUPUYTREN'S CONTRACTURE

Injectable Clostridial collagenase is a promising, investigational treatment for patients with Dupuytren's 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° to 5° of normal after the last injection were 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 durable with long-term follow up of patients from the first phase 3 clinical trial, indicating that recurrence rates are low (about 10% for MP joints and about 20% for PIP joints at 5-year follow-up). 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. US Food and Drug Administration approval for Xiaflex was granted in early 2010.

ADHESIVE CAPSULITIS (A NEW XIAFLEX INDICATION)

Adhesive capsulitis or "frozen shoulder" is a condition characterized by progressive limitation in active and passive shoulder movements, frequently accompanied by severe pain [11,19]. Movement is limited particularly in external rotation and abduction and generally occurs in the absence of known shoulder disorders. The prevalence of adhesive capsulitis in the general population is 2% to 3% [11] but is disproportionately elevated in particular patient groups such as those with thyroid disease or diabetes, where prevalence rates of about 10% have been reported [1,11] Other factors associated with adhesive capsulitis include female gender and age. As many as 70% of patients with adhesive capsulitis are women [19], and the mean age at presentation is about 56 to 59 years [10,20].

During the early stages of the disease, a diffuse glenohumeral synovitis is present, which may lead to reactive capsular fibrosis with hypertrophic, hypervascular synovitis, and scar (collagen) formation as the disease progresses [19]. A role for cytokines has been implicated in the inflammation and fibrosis which occurs in adhesive capsulitis, and transforming growth factor (TGF)–β, platelet-derived growth factor (PDGF) and hepatocyte growth factor have each been identified in capsular biopsy specimens [19]. Interestingly, TGF-α and PDGF have also been implicated in the modified myofibroblast contractility and proliferation that underlies Dupuytren's contracture [5].

Physiotherapy and mobilization are generally regarded as first-line therapy in early-stage disease, usually in combination with analgesics or nonsteroidal anti-inflammatory drugs [1]. Intra-articular corticosteroids may be considered in later stage disease; however, injection may have delayed efficacy in patients who were symptomatic for more than 5 months and should be used with caution in patients with diabetes because of their potential to interfere with glucose homeostasis [1,19]. In some patients, surgical arthroscopic capsular release is required, during which the capsular scar is divided using an electrocautery device and motorized shaver [19]. This technique is often required in patients with advanced adhesive capsulitis but is considered demanding and requires appropriate patient selection, anesthesia, and postoperative analgesia for success [19]. The investigators theorized that adhesive capsulitis was another indication for injectable Clostridial collagenase as the collagenous adhesion(s) affecting the capsule might be amenable to lysis. After study in six cadavers to assure the injection technique did not pierce the anterior capsule injection site, two recent phase 2 studies assessed the use of investigational injectable Clostridial collagenase as an effective treatment of adhesive capsulitis. Results are positive for this new indication.

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