Injectable Collagenase Clostridium Histolyticum: A New Nonsurgical Treatment for Dupuytren's Disease

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Purpose The Collagenase Option for the Reduction of Dupuytren's (CORD) II study investigated the efficacy and safety of injectable Xiaflex (collagenase clostridium histolyticum), in patients with Dupuytren's contracture.

Methods This was a prospective, randomized, placebo-controlled trial with 90-day double-blind and 9-month open-label phases. We randomized patients with contractures affecting metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints 2 to 1 to collagenase (0.58 mg) or placebo. Cords received a maximum of 3 injections. Cord disruption was attempted the day after injection using a standardized finger extension procedure. Primary end point was reduction in contracture to 0° to 5° of normal 30 days after the last injection.

Results We enrolled 66 patients; 45 cords (20 MCP to 25 PIP joints) received collagenase and 21 cords (11 MCP to 10 PIP joints) received placebo in the double-blind phase. Statistically significantly more cords injected with collagenase than placebo met the primary end point (44.4% vs 4.8%; $p <$ .001). The mean percentage decrease in degree of joint contracture from baseline to 30 days after last injection was 70.5% ± 29.2% in the collagenase group and 13.6% ± 26.1% in the placebo group ($p < .001$). The mean increase in range of motion was significantly greater in the collagenase (35.4° ± 17.8°) than in the placebo (7.6° ± 14.9°; $p < .001$) group. Efficacy after open-label treatment was similar to that after the double-blind phase: 50.7% of all joints achieved 0° to 5° of normal. More patients were satisfied with collagenase ($p < .001$). No joint had recurrence of contracture. One patient had a flexion pulley rupture and one patient underwent routine fasciectomy to address cord proliferation and sensory abnormality. No tendon ruptures or systemic allergic reactions were reported. Most adverse events were related to the injection or finger extension procedure.

Conclusions Collagenase clostridium histolyticum is the first Food and Drug Administration–approved, nonsurgical treatment option for adult Dupuytren's contracture patients with a palpable cord that is highly effective and well tolerated. *(J Hand Surg 2010;35A:2027–2038. © 2010 Published by Elsevier Inc. on behalf of the American Society for Surgery of the Hand.)*

Type of study/level of evidence Therapeutic I.

Key words Collagenase clostridium histolyticum, cord contracture, Dupuytren's contracture, enzymatic fasciotomy, recurrence.

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The authors thank Ted Smith, PhD, and Harvey Kushner, PhD, of Auxilium Pharmaceuticals, for statistical support; Dat Nguyen, PharmD, of Auxilium Pharmaceuticals; Lynn Brown, PhD, and Maribeth Bogush, PhD, of ApotheCom; and Jennifer R. Kent, PhD, of DesignWrite, for writing and editorial assistance.

Received for publication December 14, 2009; accepted in revised form August 9, 2010.

Auxilium Pharmaceuticals provided funding for this research. D.G. and S.C. own shares in Auxilium. J.K. is on the advisory board of Auxilium. Support was received in the form of per patient funding of patients processed in a clinical trial from Auxilium. N.J. is an employee of and owns stock options in Auxilium Pharmaceuticals.

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0363-5023/10/35A12-0018$36.00/0
doi:10.1016/j.jhsa.2010.08.007

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HISTORICALLY, SURGERY HAS been the most effective treatment for Dupuytren's contracture. Various procedures are used (ie, open fasciectomy, open fasciotomy, needle aponeurotomy),[1-5] although disadvantages are associated with each. Complications may occur, convalescence can be prolonged, extensive hand therapy is often needed, and disease extends or recurs in many patients.[1,6-10] In addition, not all patients with Dupuytren's contracture are appropriate candidates for surgery because of an inability to tolerate anesthesia or the intraoperative or postoperative complications that may occur.[11]

Injectable collagenase clostridium histolyticum (XIAFLEX; Auxilium Pharmaceuticals, Inc, Malvern, PA) is a Food and Drug Administration–approved, office-based, nonsurgical treatment for adult patients with Dupuytren's contracture with a palpable cord. The injectable collagenase preparation consists of 2 distinct collagenases that cleave collagen strands at different sites.[12] AUX I (a class I *C histolyticum* collagenase) cleaves the terminal ends of collagen, and AUX II (a class II *C histolyticum* collagenase) cleaves internal sections of collagen.[12] *In vitro* studies suggest that after injection into the Dupuytren's cord, the collagenases work synergistically to provide hydrolyzing activity toward collagen, weakening the contracted cord and improving elasticity and mobility.[13]

The Collagenase Option for the Reduction of Dupuytren's (CORD) I study investigated the efficacy and safety of collagenase clostridium histolyticum, and results from the 90-day phase were recently reported.[14] The CORD I study—a prospective, randomized, double-blind, placebo-controlled study conducted in the United States—demonstrated that collagenase clostridium histolyticum treatment significantly improved outcomes compared with placebo.[14] Moreover, collagenase was generally well tolerated, and no systemic allergic reactions were observed. Here, we present results from a similar study with a nearly identical protocol (CORD II), which was conducted in Australia, and discuss the similarities and differences between CORD I and CORD II findings. The objectives of CORD II were to evaluate the efficacy and safety of collagenase clostridium histolyticum in reducing the degree of contracture and to evaluate recurrence rates during a 12-month study period in patients with Dupuytren's contracture.

MATERIALS AND METHODS

Study design

The Collagenase Option for the Reduction of Dupuytren's II (CORD II) was a prospective, multicenter, phase 3 clinical study with a 90-day, randomized, double-blind, placebo-controlled phase and a 9-month open-label phase.

The study was conducted under the auspices of the human research ethics committees at each of the 5 participating centers throughout Australia, according to the ethical principles of Good Clinical Practices and according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonised Tripartite Guideline. Auxilium Pharmaceuticals, Inc, designed the study according to Regulatory Agency requirements; coordinated the activities for initiating and monitoring the study; developed the protocol, case report forms, and consent forms; and financially supported the study. The investigators collected data and Auxilium Pharmaceuticals, Inc, analyzed them. Kendle International (Edinburgh, UK) provided data management services.

Study population

Patients eligible for study participation were in good health, were 18 years of age or older, had Dupuytren's contracture of the metacarpophalangeal (MCP) joint between 20° and 100° or of the proximal interphalangeal (PIP) joint between 20° and 80° in at least 1 digit (not the thumb), and demonstrated an inability to simultaneously place the affected finger and palm flat on a table. Women were required to be postmenopausal or using contraception. Exclusion criteria included breastfeeding or pregnancy; bleeding disorder; recent stroke; previous treatment of the primary joint within 90 days of first dose of study drug; collagenase treatment or treatment with any investigational drug within 30 days of first dose of study drug; use of a tetracycline derivative within 14 days of first dose of study drug (because tetracycline derivatives may inhibit the collagenolytic activity of mammalian collagenase homologs [ie, matrix metalloproteinases])[15-17]; anticoagulant within 7 days of first dose of study drug (with the exception of low-dose aspirin); allergy to collagenase; and chronic muscular, neurologic, or neuromuscular disorders affecting the hands. Patients with recurrent disease were eligible for study participation if other eligibility criteria were met. All patients provided written informed consent.

We conducted the study between August 2007 and September 2008. We screened 72 patients and enrolled 66 in the study. We achieved randomization with the use of a computer-generated permuted block design (block size of 6) within each baseline severity level for each study site. Patients were randomly assigned to receive collagenase or placebo in the double-blind

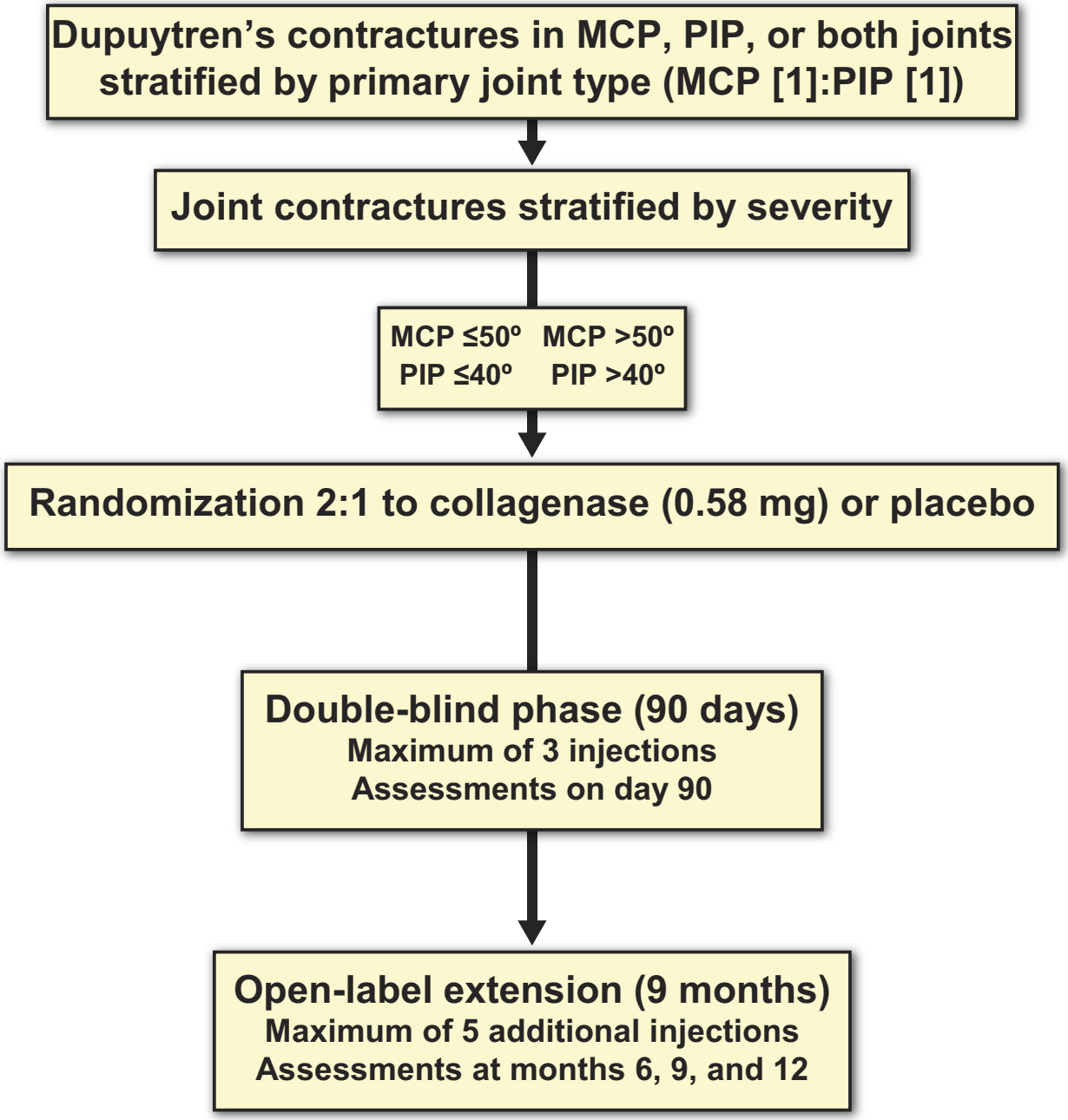

FIGURE 1: Study design and stratification and randomization in double-blind phase and extension to an open-label phase.

phase in a 2:1 ratio, to maximize the number of patients who could benefit with active treatment versus placebo (Fig. 1). There were 45 actively treated (MCP:PIP, 20:25) and 21 placebo-treated (MCP:PIP, 11:10) primary joints during the double-blind phase. For primary joints, more PIP than MCP joint contractures were categorized as high severity at baseline. In the PIP group, 7 of 35 contractures were low in severity (40° or less) and 28 of 35 were high in severity (greater than 40°). In contrast, MCP joint contractures were almost evenly divided in severity between low (50° or less, 17 of 31) and high (greater than 50°, 14 of 31).

Two patients in the placebo group prematurely discontinued (withdrew consent): one after receiving one injection and one after receiving 2 injections. All patients were included in the intent-to-treat and safety analyses.

All 64 patients who completed the double-blind phase entered the open-label phase. Of these, 58 completed the phase and 6 prematurely discontin-

TABLE 1. Baseline Patient Characteristics

Characteristic	Collagenase (n = 45)	Placebo (n = 21)	Total (N = 66)	p Value[¶]
Mean age (y [SD])	63.0 (7.8)	65.5 (11.1)	63.8 (9.0)	.28
Male (n [%])	39 (86.7)	17 (81.0)	56 (84.8)	.71
White, non-Hispanic ethnicity (n [%])*	45 (100.0)	21 (100.0)	66 (100.0)	
Total contracture index[†]				
Mean (SD)	174.7 (107.2)	150.1 (84.0)	166.9 (100.4)	.36
Median (range)	145.0 (25–525)	140.0 (50–335)	142.5 (25–525)	
Bilateral hand contracture (n [%])[‡]	22 (48.9)	12 (57.1)	34 (51.5)	
Affected joints[‡] per patient				
Mean (SD)	3.4 (2.3)	3.0 (1.5)	3.3 (2.1)	.40
Range	1–11	1–5	1–11	
Affected MCP joints[‡] per patient				
Mean (SD)	1.5 (1.6)	1.5 (1.5)	1.5 (1.5)	.89
Range	0–7	0–5	0–7	
Affected PIP joints[‡] per patient				
Mean (SD)	2.0 (1.6)	1.4 (1.2)	1.8 (1.5)	.18
Range	0–7	0–4	0–7	
Family history of Dupuytren's disease (n [%])	22 (48.9)	9 (42.9)	31 (47.0)	.79
Duration of symptoms when medical treatment first sought (mo)				
Mean (SD)	68.1 (85.0)	68.3 (81.6)	68.2 (83.3)	.99
Median (range)	36.0 (2–360)	48.0 (3–360)	36.0 (2–360)	
Prior treatment for Dupuytren's disease (n [%])				
None	21 (46.7)	10 (47.6)	31 (47.0)	1.0
Surgery in either hand[§]	24 (53.3)	11 (52.4)	35 (53.0)	1.0
Hand therapy	4 (8.9)	1 (4.8)	5 (7.6)	1.0
Injection	0	0	0	

*Race or ethnic group was self-reported.
[†]The total contracture index is the sum of fixed-flexion contractures (20° or greater, caused by a Dupuytren's cord) in all affected joints (maximum of 16 joints per patient) measured at screening.
[‡]The affected number of joints per patient is the number of joints at screening with fixed-flexion contractures of 20° or greater caused by Dupuytren's cord.
[§]Primarily standard fasciotomies.
[¶]We used Fisher's exact test for categorical comparisons and *t*-tests for numerical comparisons.

ued it (all were lost to follow-up). Of the 6 patients who prematurely discontinued, one received placebo in the double-blind phase and never received collagenase in the open-label phase. Throughout the entire 12-month study of both the double-blind and open-label phases, 63 patients had 134 Dupuytren's cords injected with collagenase; 57 of 63 patients completed the 12-month study. Mean duration of study participation from the first dose of collagenase was 311 ± 82 days (range, 56–379 d).

A total of 47 patients had 89 Dupuytren's cords from nonprimary joints injected with collagenase during the double-blind phase or open-label phase of the study, or both, including 15 of the 21 placebo-injected cords from primary joints that were eligible to receive collagenase during the open-label phase.

Demographic characteristics and disease severity at baseline were similar between the 2 treatment groups (Table 1). Duration of disease significantly correlated with severity of baseline contracture. In patients with low baseline contracture severity, duration of disease was lower compared with patients with high baseline contracture severity (9.1 ± 6.3 vs 15.1 ± 10.6 y; p = .008). Thus, stratification of patients by baseline severity balanced study groups by both severity and duration of disease.

Treatment

Before initiating treatment, investigators prioritized the joints affected by Dupuytren's cords by selecting which joint would be treated first, second, and third. Joints affected by Dupuytren's cords treated first were considered primary joints; those treated second and third were considered nonprimary joints. Physicians were instructed to choose a Dupuytren's cord affecting the MCP joint for injection when a combination of both MCP and PIP joints were contracted in the same finger. Primary joints were stratified by type (MCP or PIP in a 1:1 ratio) and by severity of joint contracture, and then randomized 2:1 to receive collagenase clostridium histolyticum or placebo.

We reconstituted collagenase clostridium histolyticum (0.58 mg per injection plus lyophilized Tris and sucrose) and placebo (lyophilized Tris and sucrose only) in sterile diluent. Collagenase and placebo solutions were injected directly into Dupuytren's affected cords, as previously described by Hurst et al.[14] When needed, a standardized finger extension procedure was implemented up to 3 times the day after injection to facilitate cord disruption.[14] After the finger extension procedure, patients were instructed to wear night splints for up to 4 months, perform at-home finger flexion and extension exercises, and return to normal daily activities. Follow-up visits occurred 1, 7, and 30 days postinjection.

Treatment cycles

A treatment cycle consisted of injection, finger extension, and 30-day follow-up.[14] Each affected cord could undergo a maximum of 3 treatment cycles in 30-day intervals, and each patient could receive a maximum of 8 treatment cycles during the 12-month study. During the 90-day double-blind phase, if the primary joint (first treated joint) met the primary end point (defined below) in fewer than 3 treatment cycles, a second joint could be treated. If the first and second joints met the primary end point with one treatment cycle each, a third joint could be treated.

During the 9-month open-label phase, treatment was at the discretion of the investigator. Patients from the double-blind phase who still required collagenase treatment could receive up to 5 additional collagenase injections in the open-label phase. These included patients who received placebo treatment, patients who did not achieve clinical success with fewer than 3 collagenase injections, and patients who had other Dupuytren's cords that were not injected with collagenase. Patients in the open-label phase were observed for an additional 9 months, which increased the duration of collagenase efficacy and safety assessments to a total of 12 months.

Assessments

Study assessments are summarized in the Appendix (this Appendix can be viewed at the *Journal's* Web site at www.jhandsurg.org). We measured fixed-flexion angles using a standardized finger goniometry protocol after fingers were passively extended until a static end point was reached. We measured fixed flexion deformities to ascertain the degree of correction. Full flexion was measured with maximum contraction of the treated fingers with an injected Dupuytren's cord. We assessed grip strength using dynamometry. We measured angles of extension-flexion and grip strength at screening and at various times during the double-blind and open-label phases of the study.

The primary end point was reduction in primary joint (MCP or PIP) contracture to 0° to 5° of normal 30 days after the last injection. We also performed all analyses by joint type (ie, MCP or PIP). We evaluated recurrence of contracture, defined as an increase in joint contracture to 20° or greater in the presence of a palpable cord at any time during the study in joints that attained a reduction in contracture to 0° to 5° of normal, in the open-label phase.

Safety assessments included monitoring vital signs and collecting blood and urine samples for immunologic measurements and routine clinical laboratory tests (Appendix; this Appendix can be viewed at the *Journal's* Web site at www.jhs.org). A 60-minute observation period followed each injection. Patients were monitored for local and systemic adverse events (AEs), which were assessed for severity and relationship to study treatment.

We used a validated enzyme-linked immunogenicity assay to detect the presence of antibodies against class I *C histolyticum* collagenase (AUX-I), class II *C histolyticum* collagenase (AUX-II), or both, in serum samples that were collected at screening and 30 days after each injection, and then quarterly in the open-label phase. When we detected antibodies, we quantified titers using a titer determination assay.

Statistical analyses

Efficacy results were reported as primary joints (double-blind phase) and nonprimary joints (double-blind and open-label phases). We performed analysis of the primary end point using the Cochran-Mantel-Haenszel test, controlling for joint type and baseline contracture severity. All numerically continuous data are presented as mean (±SD) unless stated otherwise. We compared

TABLE 2. Treatment Outcomes During the 90-Day Double-Blind Phase

Outcome	Collagenase Treatment	Placebo Treatment	p Value
Primary end point: reduction in contracture to 0° to 5° of normal 30 days after last injection (n [%])			
All primary joints	20/45 (44.4)	1/21 (4.8)	<.001
Primary MCP joints	13/20 (65.0)	1/11 (9.1)	.003
Primary PIP joints	7/25 (28.0)	0/10	.069
Secondary end points (30 d after last injection)—all primary joints			
Clinical improvement* (n [%])	35/45 (77.8)	3/21 (14.3)	<.001
Mean change in contracture from baseline (%)	70.5 ± 29.2	13.6 ± 26.1	<.001
Median time to reduction in contracture to 0° to 5° of normal (d)	57	NC	<.001
Mean change in range of motion from baseline† (°)	35.4 ± 17.8	7.6 ± 14.9	<.001

NC, median could not be calculated.
*Clinical improvement was defined as a reduction in contracture of 50% or more from baseline.
†The mean change in range of motion from baseline was defined as the difference between full-flexion and full-extension angles.

AEs between treatment groups using Fisher's exact test. All reported p values were 2-sided. All p values that were computed to be less than .001 were reported only as $p < .001$. All analyses were performed using SAS (Cary, NC), version 9.1.

RESULTS

Efficacy

Primary joints in the double-blind phase: Significantly more primary joints in the collagenase group than in the placebo group had a reduction in contracture to 0° to 5° of normal 30 days after the last injection (44.4% vs 4.8%; $p < .001$) (Table 2, Fig. 2). A median of 57 days was needed to reach the primary end point in the collagenase group ($p < .001$). Among the 20 primary joints that reached the primary end point in the collagenase group, a mean of 1.5 injections were needed. Of the joints in the collagenase group that did not meet the primary end point (n = 25), most (17 of 25) did not receive 3 injections into the Dupuytren's cord, most commonly because investigators reported "no palpable cord to inject."

When analyzed according to joint type, significantly more MCP joints in the collagenase group had a reduction in contracture to 0° to 5° of normal 30 days after the last injection than those in the placebo group (13 of 20 vs 1 of 11, respectively; $p = .003$) (Table 2, Fig. 2). More PIP joints met the primary end point in the collagenase group than in the placebo group, but statistical significance was not reached (7 of 25 vs 0 of 10, respectively; $p = .069$) (Table 2, Fig. 2).

Prior surgery for Dupuytren's contracture did not affect attainment of the primary end point. The proportion of patients who had prior surgery for Dupuytren's contracture was not statistically different among those who reached the primary end point (9 of 20) and those who did not (15 of 25; $p = .38$).

Conversely, 21 patients had undergone surgery for Dupuytren's contracture previously and 24 patients had not. The primary end point was attained in 11 of 21 and 9 of 24 of these patients, respectively. Of the 21 patients who had surgery previously, 14 had surgery in the same hand as the collagenase injection. Of these patients, the primary end point was attained in 5 of 14. Nine of the 14 patients had surgery in the same hand and finger as the collagenase injection, and 3 of 9 of these patients attained the primary end point. At the time of the 12-month follow-up, none of the 20 successfully treated cords had experienced a recurrence.

Joints with low baseline contracture severity responded better to injection of Dupuytren's cords with collagenase than those with high baseline contracture severity (Fig. 3). Because the duration of disease is significantly lower in patients with lower baseline contracture severity, this suggests that earlier treatment may be indicated to promote improved contracture responses. In the collagenase group, mean contracture was reduced from 49.5° at baseline to 7.5° in MCP joints and from 56.2° at baseline to 24.0° in PIP joints. In comparison, little change in contracture was observed in MCP (from 46.8° at baseline to 41.4°) or PIP joints (from 53.5° at baseline to 47.5°) in the placebo group.

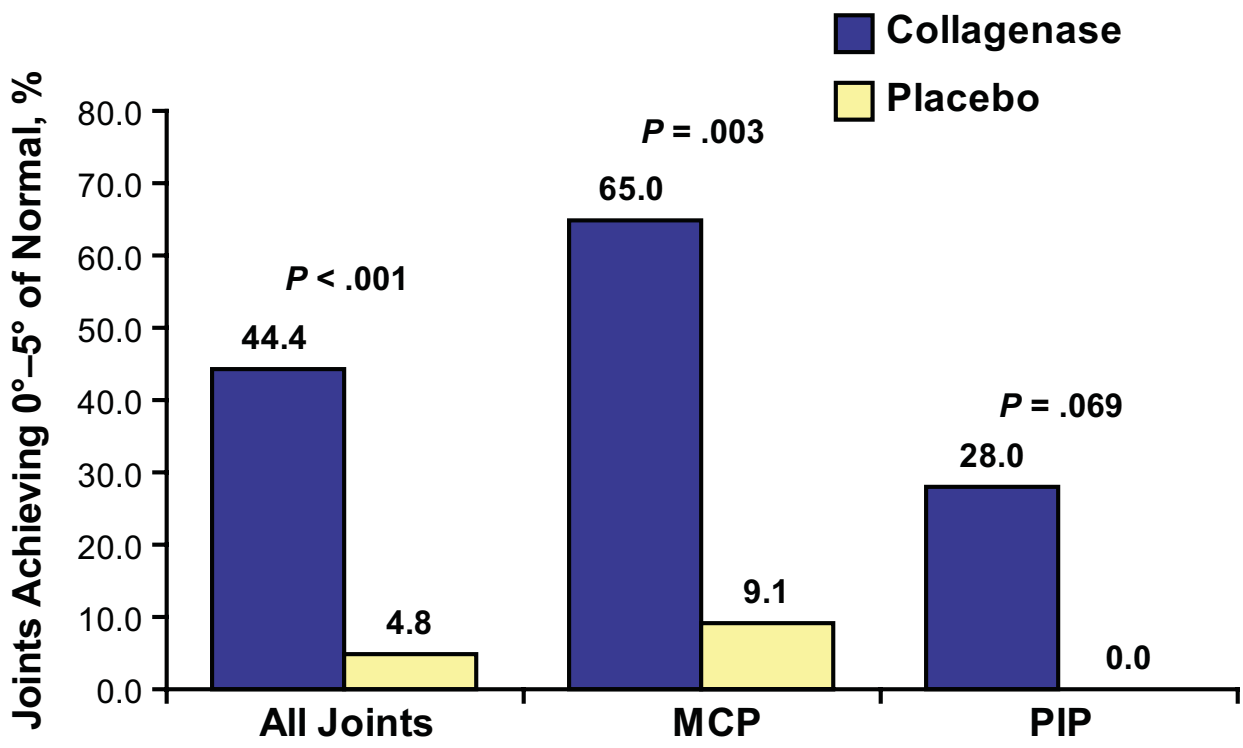

FIGURE 2: Reduction in contracture to 0° to 5° of normal 30 days after the last injection in the double-blind phase.

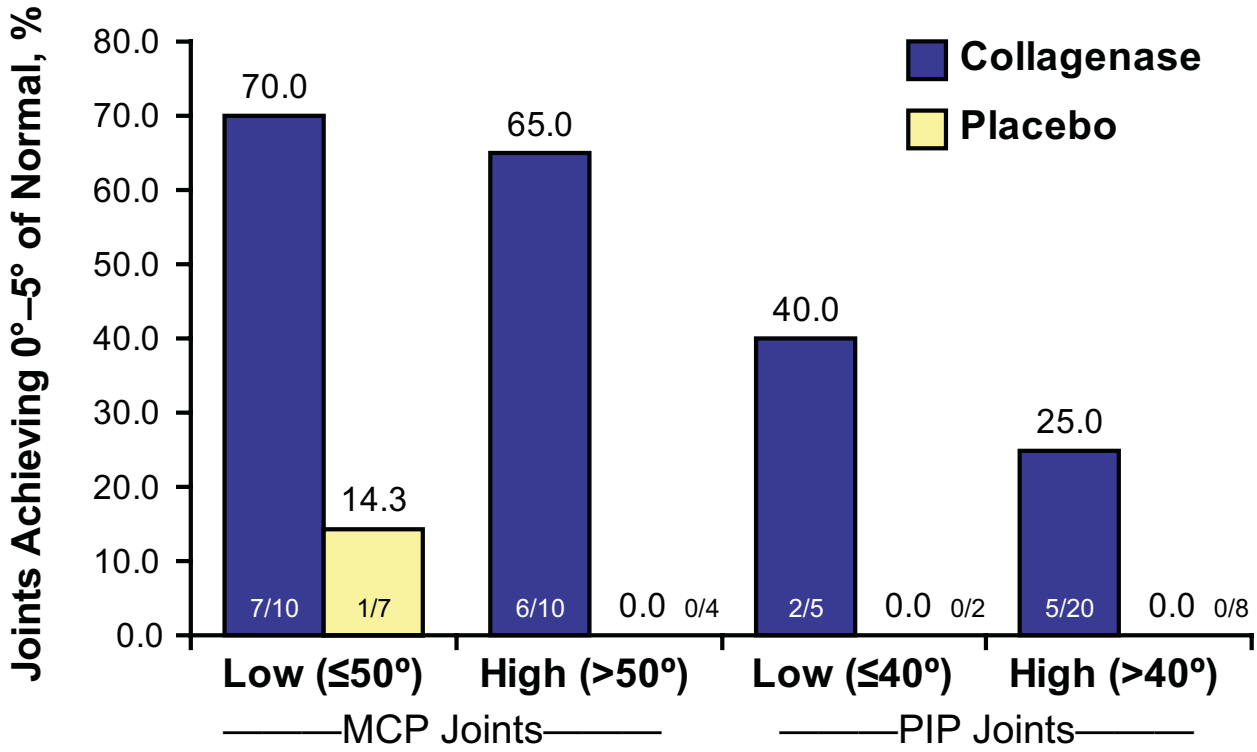

FIGURE 3: Reduction in contracture to 0° to 5° of normal 30 days after the last injection in the double-blind phase, according to baseline contracture severity.

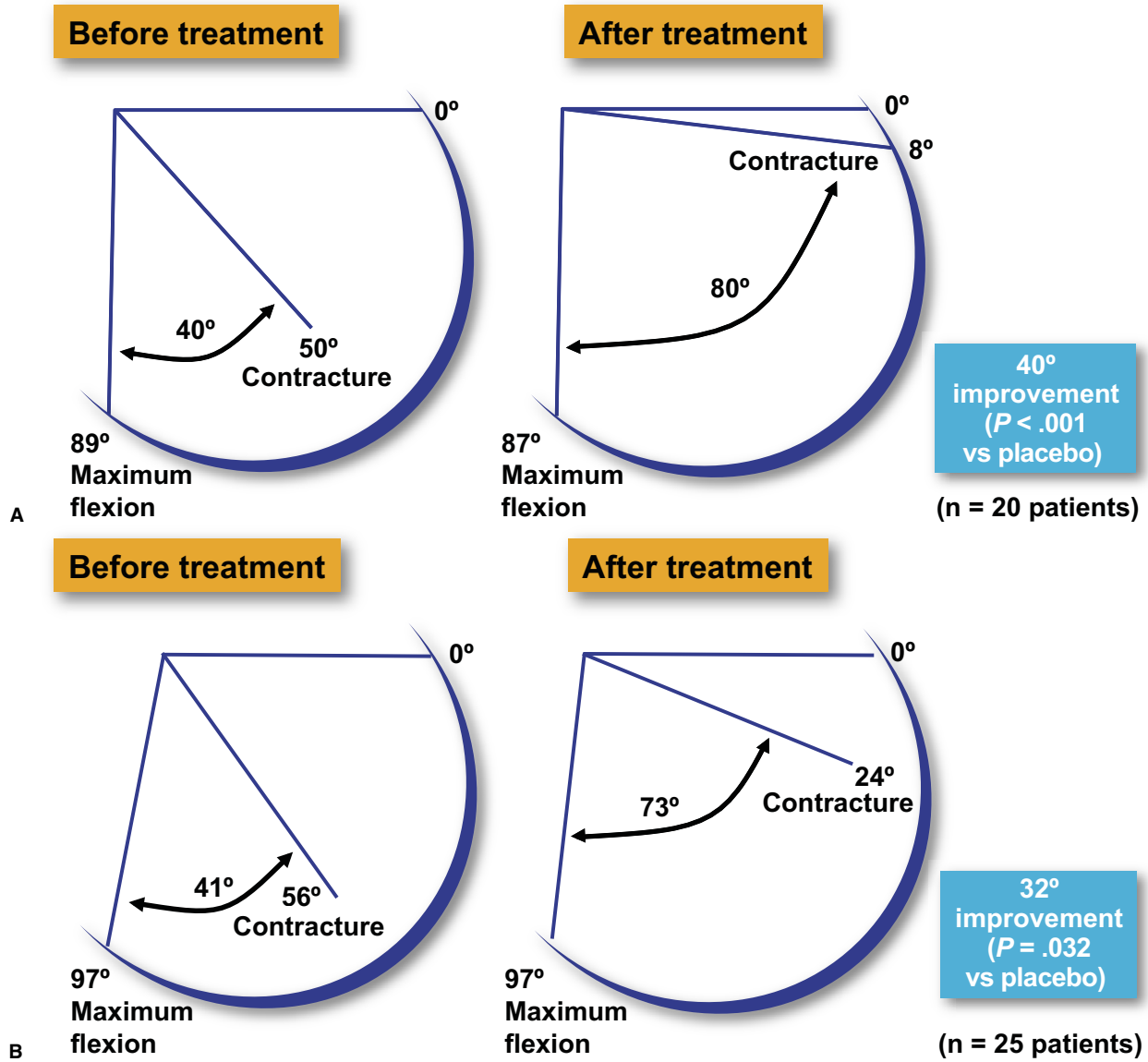

FIGURE 4: Change in range of motion from baseline in **A** MP and **B** PIP joints with Dupuytren's cords injected with collagenase in the double-blind phase.

Change in range of motion from baseline was significantly better in the collagenase group than in the placebo group. Compared with joints in the placebo group (7.6° improvement), mean range of motion improved 40° in MCP joints ($p < .001$) and 32° in PIP joints ($p = .032$) (Fig. 4).

All joints: combined 12-month data: In total, we injected 134 Dupuytren's cords from 134 joints with collagenase during the 12-month study: 62 cords affected MCP joints and 72 cords affected PIP joints (Table 3). The proportion of joints with Dupuytren's cords injected with collagenase that had a reduction in contracture to 0° to 5° of normal 30 days after the last injection was 68 of 134 overall: 42 of 62 for MCP joints and 26 of 72 for PIP joints.

Recurrence

We defined recurrence as an increase in joint contracture to 20° or greater in the presence of a palpable cord at any time during the study in joints that attained a reduction in contracture to 0° to 5° of normal. No joint met the criteria for recurrence of contracture by the end of the 12-month study. This included 20 primary joints with Dupuytren's cords injected with collagenase in the double-blind phase and 48 joints with Dupuytren's cords injected with collagenase in the double-blind phase, open-label phase, or both.

TABLE 3. Baseline Severity of All Joints in the Double-Blind Study and Open-Label Phase

	All Joints		MCP Joints		PIP Joints	
	Low	High	Low (≤50)	High (>50)	Low (≤40)	High (>40)
Cords injected with collagenase (n [% of total])	73 (54.5)	61 (45.5)	44 (32.8)	18 (13.4)	29 (21.6)	43 (32.1)
0° to 5° (n [%])	49 (67.1)	19 (31.1)	31 (70.5)	11 (61.1)	18 (62.1)	8 (18.6)
Mean change (% [SD])*	75.8 (30.4)	58.1 (33.6)	78.7 (29.4)	81.4 (23.9)	71.5 (32.0)	48.3 (32.4)

*Mean change (% [SD]) in degree of contracture from baseline to after the last injection of collagenase. All joints were treated with collagenase.

TABLE 4. Treatment-Related Adverse Events Occurring in 5% or More of Patients During the Double-Blind Phase and the 12-Month Study (Both Double-Blind and Open-Label Phases)

	Double-Blind Phase		12-Mo Study
	Collagenase (n = 45)	Placebo (n = 21)	Collagenase (n = 63)
Patients with ≥1 treatment-related adverse event (n [%])*	45 (100.0)	8 (38.1)	63 (100.0)
Edema, peripheral†	35 (77.8)	2 (9.5)‡	54 (85.7)
Contusion	33 (73.3)	2 (9.5)‡	46 (73.0)
Pain in extremity	22 (48.9)	2 (9.5)‡	34 (54.0)
Injection site pain	17 (37.8)	2 (9.5)‡	28 (44.4)
Injection site hemorrhage	19 (42.2)	0‡	27 (42.9)
Injection site swelling	16 (35.6)	3 (14.3)	23 (36.5)
Tenderness	6 (13.3)	0	20 (31.7)
Pruritus	5 (11.1)	0	13 (20.6)
Lymphadenopathy	11 (24.4)	0‡	13 (20.6)
Axillary pain	5 (11.1)	0	7 (11.1)
Injection site vesicles	2 (4.4)	0	5 (7.9)

*In the double-blind phase, 66 patients had 94 Dupuytren's cords treated with 166 injections (106 collagenase and 60 placebo). In the 12-month study, 63 patients received at least 1 injection of collagenase, and 134 Dupuytren's cords were treated with 221 injections of collagenase.
†Edema of the treated extremity, not diffuse edema in all extremities.
‡$p \leq .05$; double-blind phase only; collagenase versus placebo, based on Fisher's exact test.

Safety

Overall, all patients who received collagenase in the double-blind phase reported at least one treatment-related AE, compared with 8 of 21 placebo-treated patients (Table 4). Patients who received collagenase had significantly higher rates of edema peripheral (mostly swelling of the treated hand), contusion, extremity pain, injection site hemorrhage, injection site pain, and lymphadenopathy than those who received placebo (all comparisons, $p < .05$). Grip strength and flexion were not affected. Most treatment-related AEs were mild or moderate in intensity and resolved without intervention within a median of 8 to 10 days (placebo, 8 d; collagenase, 10 d). One serious treatment-related AE was reported: a patient had a flexion pulley rupture of the left small finger and subsequently underwent PIP joint arthrodesis and tenotomy.

In the double-blind phase, no patients in the collagenase group who had prior surgery for Dupuytren's contracture (n = 24) had serious AEs after injection. The distribution and severity of AEs after collagenase injection were comparable between patients with and without prior surgery for Dupuytren's contracture.

Safety during the 12-month study was similar to that observed during the double-blind phase (Table 4). One patient had 2 serious AEs that were considered related to the study drug: proliferation of Dupuytren's cord (ie, rapid thickening of the

treated cord without a change in length) and sensory abnormality in the treated hand. This patient subsequently underwent a routine fasciectomy; removal of the cord tissue resolved the sensory abnormality. No arterial, nerve, or tendon injuries were reported during the 12-month study.

Immunogenicity

Most patients had detectable antibodies to AUX-I (40 of 42; 95.2%) and AUX-II (37 of 42; 88.2%) approximately 30 days after the first injection of collagenase. By the third injection, all patients in the collagenase group had detectable antibodies to AUX-I and AUX-II; however, no severe systemic allergic reactions were reported.

DISCUSSION

Results from the CORD II study support the long-term (ie, 12-mo) efficacy and safety of collagenase clostridium histolyticum in the treatment of patients with Dupuytren's contracture. In this study, significantly more joints in the collagenase group attained a reduction of contracture to 0° to 5° of normal 30 days after the last injection, compared with the placebo group. The primary end point in this study was strict, and some patients and physicians may be satisfied with lesser degrees of improvement. Patient satisfaction and physician ratings of improvement after treatment with collagenase were significantly higher than with placebo treatment, which is an important consideration because Dupuytren's contracture often has a negative impact on patients' lives. Also, patient satisfaction and physician ratings of improvement were shown to correlate with joint range of motion. In addition, no patient had recurrence of a successfully treated joint during the time of this study. Prospective patient follow-up during the next 5 years will provide additional information about recurrence after collagenase treatment.[18]

One patient in the placebo group who had Dupuytren's contracture (25° at baseline) for 6 months attained a reduction of contracture to 0° to 5° of normal 30 days after the last injection. Reasons for this successful outcome are unknown; possibly, the injection procedure combined with the finger extension procedure weakened the Dupuytren's cord. In addition, splinting the finger at night and performing finger flexion and extension exercises at home might have improved the range of motion for some placebo-treated cords in the placebo group.

The proportion of nonprimary PIP joints that attained a reduction of contracture to 0° to 5° of normal was somewhat higher (19 of 47) than the primary PIP joints in the double-blind phase (7 of 25). We observed a discordance in baseline severity of PIP joints between the 2 phases of the study, with a higher proportion of high-severity PIP joints in the double-blind phase compared with the open-label phase (20 of 25 vs 23 of 47, respectively). This may have slightly lowered double-blind efficacy results versus the open-label results, because contracture of high-severity PIP joints is typically harder to correct.[3,8]

Collagenase treatment was well tolerated. Most AEs were related to the injection or finger extension procedure, were mild or moderate in intensity, and resolved without intervention. The type and intensity of treatment-related AEs during the 90-day, double-blind phase were similar to those observed during the open-label phase. No tendon ruptures, nerve injuries, evidence of systemic allergic reactions, or artery injuries were reported. However, one patient had a flexion pulley rupture. No unexpected AEs occurred; the type and intensity of treatment-related AEs that occurred during the first 90 days of collagenase treatment in CORD II are similar to those observed in CORD I.[14]

Findings from CORD II agree with those reported for CORD I.[14] Joints with low baseline contracture severity responded better to injection of Dupuytren's cords with collagenase than those with high baseline contracture severity. The proportion of joints that attained a reduction of contracture to 0° to 5° of normal 90 days after injection of Dupuytren's cords with collagenase was lower in CORD II than in CORD I, both overall (44% vs 64%) and when evaluated according to joint type (MCP [65% vs 76.7%, respectively]; PIP [28% vs 40.0%, respectively]).[14] Lower overall efficacy in CORD II may have resulted from differences in MCP to PIP stratification compared with the CORD I study (1:1 stratification by joint [MCP to PIP] in CORD II and 2:1 stratification in CORD I) or a greater proportion of high-severity PIP joints studied. However, the proportion of joints achieving a reduction of contracture to 15° or less was similar in CORD I (74%) (Curtin and Naam, presented at the 40th Annual Scientific Meeting of the American Association for Hand Surgery, 2010) and CORD II (67%), which indicates that the efficacy observed in these studies may be more comparable than the primary end point alone suggests.[14]

Surgery is currently the most widely employed treatment for Dupuytren's contracture.[19,20] The decision to perform surgery on joint contractures is based on contracture measurement and functional impairment.[19–21] Recuperation from surgery can be long as a result of complications such as tendon rupture (0.2% of patients), digital nerve injury (1.7% to 7.8% of patients), digital artery injury (1.9% to 9.7% of patients), and infection (1.0% to

10.6% of patients).[1,3,6,10] In addition, extensive hand therapy is often needed, particularly with more invasive procedures (ie, fasciectomy) and disease extension or recurrence occurs in many patients.[1,5-10]

Dupuytren's contracture may also be corrected with less-invasive procedures such as percutaneous needle aponeurotomy. Unfortunately, published data reporting the efficacy and safety of this technique are limited. In the few existing reports, short-term efficacy is good (better for MCP than for PIP joints); however, complications have been known to occur.[4,5,22-24]

Limited long-term efficacy and the potential for serious complications associated with surgery and percutaneous needle aponeurotomy underscore the need for simpler, less-invasive treatment options that are effective and safe and cause minimal convalescence. Nonsurgical treatment options such as radiation therapy, vitamin E, and local injection therapy using interferon or corticosteroids have had limited success.[25] As early as 1965, noncollagenase enzymatic fasciotomies with preparations including trypsin, hyaluronidase, and lidocaine were attempted, also with limited success.[26,27] Disruption of the Dupuytren's cord could be attained with forceful finger extension, but small sample sizes, lack of follow-up, and insufficient efficacy and safety measurements failed to prove that noncollagenase enzymatic fasciotomy had substantial benefits over standard surgical approaches.[25-27] More recently, inhibition of transforming growth factor–β1 and matrix metalloproteinase activity have been proposed as potential nonsurgical therapeutic targets for Dupuytren's disease in preclinical studies.[28-31]

Collagenase *C histolyticum* is the first nonsurgical, office-based treatment option for Dupuytren's disease with proven efficacy and safety. The CORD studies are the largest prospective, placebo-controlled studies conducted in patients with Dupuytren's disease to date. These 2 studies of 374 patients have shown that collagenase reduces Dupuytren's disease from baseline to 0° to 5° of normal in 44% to 64% of joints and to 15° or less in 67% to 74% of joints in CORD II and I, respectively, and that response to placebo is minimal (Curtin and Naam, presented at the 40th Annual Scientific Meeting of the American Association for Hand Surgery, 2010).

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APPENDIX. Study Assessments

	Double-Blind Phase									
		Injection Day		Days After Each Injection				Open-Label Phase Follow-Up		
Assessment	Screening	Before Each Injection	After Each Injection	1	7	30	Day 90	Month 6	Month 9	Month 12
Finger goniometry	X	X		X	X	X	X	X	X	X
Clinical laboratories	X					X	X			X
Immunogenicity sample		X				X	X	X	X	X
Adverse event recording	X	X	X	X	X	X	X	X	X	X
Physician/patient global assessments		X					X			X

Contracture severity was rated using a 4-point scale: 1 = normal, 2 = mild, 3 = moderate, 4 = severe. Change in contracture from baseline was rated using a 7-point scale: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. Percentage improvement in contracture was rated using a scale of 0% to 100%, where 0% indicated no improvement and 100% indicated total improvement. Satisfaction with treatment was rated using a 5-point scale: 1 = very satisfied, 2 = quite satisfied, 3 = neither satisfied nor dissatisfied, 4 = quite dissatisfied, 5 = very dissatisfied.