Efficacy and Safety of Injectable Mixed Collagenase Subtypes in the Treatment of Dupuytren's Contracture

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Purpose: To further evaluate the efficacy and safety of an injectable mixed subtype collagenase for the treatment of Dupuytren's contracture (DC).

Methods: Patients with flexion deformities of the metacarpophalangeal (MCP) and/or the proximal interphalangeal (PIP) joints of 20° or greater were randomized in a double-blind, placebo-controlled trial. Patients completing this phase could enter an open-label extension phase. The primary efficacy variable was clinical success: contracture correction to within 5° of normal (normal, 0°). Additional efficacy variables included the time and number of injections required to achieve success in the primary joint. Recurrence of contracture to 20° or greater in successfully treated joints and adverse events (AEs) were recorded.

Results: Thirty-three of 35 patients (mean ± SD, 61 ± 9 y) entering the double-blind phase completed the study; 19 of them entered the open-label extension. In the double-blind phase, clinical success of the primary joint was achieved in 16 of 23 patients receiving 1 injection and in 21 of 23 patients receiving 3 injections. No placebo-treated patients achieved joint correction. In the open-label extension, 17 of 19 patients achieved clinical success in at least 1 joint. The mean number of injections for clinical success in the double-blind and extension phases was 1.5 and 1.4, respectively; the time to clinical success ranged between 1 and 29 days. Overall, of 62 joints (31 MCP, 31 PIP) treated in 35 patients, 54 joints achieved clinical success. Over the 24-month follow-up period after the last injection, 5 joints had a recurrence. The most frequent treatment-related AEs were local reactions to injections. AEs were mild and resolved over several weeks. There were no serious treatment-related AEs.

Conclusions: The collagenase injections safely and effectively corrected MCP and PIP contractures in patients with 1 or more DC-affected joints. Recurrence rates after treatment appear to be low. Data suggest that this collagenase appears to be a viable nonsurgical treatment option for DC. (J Hand Surg 2007;32A:767–774. Copyright © 2007 by the American Society for Surgery of the Hand.)

Type of study/level of evidence: Therapeutic I.

Key words: Dupuytren's contracture, mixed collagenase subtypes.

Dupuytren's contracture (DC) is a slowly progressive[1–3] connective tissue disorder that affects the palmar fascia. At present, the cause of DC has not been established, but as myofibroblast-mediated nodules and collagen deposits develop in the palm, is the result is the pathogenic cord. With time, contracture of this cord causes the finger to flex progressively, resulting in impaired hand function and deformity.

The prevalence of DC has not been studied extensively. Global prevalence is estimated to range between 3% and 40% and generally is more prevalent among whites of Northern European ancestry than blacks, although the data are sparse on ethnic prevalence.[4,5] A large study that monitored 9,938 patients with DC among US veterans between 1986 and 1995[6] showed that although the prevalence of DC was approximately 5.5 times greater in white than in black veterans, the disease characteristics (age at onset, predominant digit affected, association with other diseases) were similar among whites and blacks. DC most frequently affects the ring finger

and the small finger,[7,8] and the most commonly affected joints in the hand are the metacarpophalangeal (MCP) and the proximal interphalangeal (PIP) joints. Prevalence rates increase with age in both men and women, but DC occurs approximately 10 years earlier and more often in men than in women.[4,5,9]

Contractures may be corrected surgically by dividing the cord or performing a fasciectomy to restore function and correct the deformity. One recent study noted a 77% improvement in classification scores immediately after surgery, but at 32 months the recurrence rate was 65%.[10] Surgery is not a cure, nor does it stop progression. Reported contracture recurrence rates after surgery vary widely, from 27% to 80%.[11–14] In addition, surgery often is accompanied by complications,[15] the most common of which is postoperative joint stiffness.[13]

Various nonsurgical treatments have been evaluated, including radiotherapy, dimethylsulfoxide injections, topical vitamin A and E application, physical therapy, ultrasonic therapy, corticosteroid injections, 5-fluorouracil treatment, and gamma interferon injections. These generally were found to be ineffective or not suitable for clinical use.[16] Phase II clinical trials, however, in which injections of mixed collagenase subtypes as treatment for DC have provided encouraging results. Collagenase acts to lyse and facilitate rupture of Dupuytren's cords in MCP- and PIP-contracted joints.[17,18]

In an open-label trial, 30 of 34 (88%) MCP joints treated with collagenase were corrected to full extension (0°) or within 5° of full extension. For PIP joints, 4 of 9 (44%) achieved full extension, whereas 3 additional PIP joints were corrected to within 15° of full extension.[17] Corrections occurred within 2 weeks after the first injection of collagenase. During the 2-year follow-up period, there were recurrences in 3 MCP joints[17]; these 3 joints with initial contractures of 30°, 40°, and 55° had recurrent contractures to 20°, 25°, and 25°, respectively.

In a placebo-controlled trial, 10,000 U of collagenase was established as the minimal safe and effective dose.[18] The clinical success rate after collagenase injections (correction to within 5° of normal extension) was 91 for MCP joints and 38 for PIP joints (1 blinded injection and a mean of 3 open-label injections) versus 0% for placebo ($p < .05$). For MCP joints, the mean follow-up period was 2 years, and there was 1 recurrence. For PIP joints, the mean follow-up period was 12.5 months, and there was 1 recurrence.

Results from these phase II trials suggest that collagenase injections are a safe and effective therapy for DC. In this study, we evaluated the efficacy of collagenase injection therapy for DC in a phase III, double-blind, placebo-controlled trial followed by an open-label extension phase with a follow-up period of up to 12 months after the last injection.

Materials and Methods

Thirty-five patients were enrolled in the study (28 men, 7 women; mean age, 61 ± 8.5 y; mean baseline MCP joint contracture, 51° ± 12°; mean baseline PIP joint contracture, 46° ± 14°; range of contractors, 20°–90°) (Table 1). Fifty-five digits were injected. In the controlled phase, 12 small, 8 ring, 4 middle, and 2 index digits were injected in 16 right and 10 left hands. In the open-label phase, 12 small, 8 ring, 4 middle, and 3 index digits were injected in 10 right and 17 left hands. Also, one left ring and one right small finger were treated in both the blinded and open-label phases. More than one digit was involved in 10 patients in the controlled phase and in 8 patients in the open-label phase. No thumbs were treated.

Table 1. Baseline Demographics

	Collagenase (N = 23)	Placebo (N = 12)	Total (N = 35)
Age, y (mean ± SD)	60.1 ± 7.6	63.8 ± 10.0	61.3 ± 8.5
Gender, n (%)			
Male	20 (87)	8 (67)	28 (80)
Female	3 (13)	4 (33)	7 (20)
Race, n (%)			
White	23 (100)	12 (100)	35 (100)
Weight, lb (mean ± SD)	187.3 ± 32.1	176.8 ± 30.8	183.7 ± 31.6
Height, in (mean ± SD)	69.8 ± 2.2	69.6 ± 3.5	69.8 ± 2.7
Degree of baseline contracture, n (mean ± SD)			
MCP + PIP	23 (52.0 ± 13.4)	12 (43.8 ± 10.9)	35 (49.1 ± 13.0)
MCP	14 (53.2 ± 11.9)	7 (47.1 ± 12.5)	35 (51.2 ± 12.1)
PIP	9 (50.0 ± 16.0)	5 (39.0 ± 6.5)	14 (46.1 ± 14.2)

Eight patients had bilateral disease. Two of these were treated in the controlled phase and 6 were treated in the open-label phase. Thirteen men and 4 women had a positive family history of DC. Seven men had Garrod's pads and 9 men had Ledderhose's disease.

The overall study design consisted of a phase III, randomized, double-blind, placebo-controlled trial followed by an open-label extension. Enrolled patients (age, ≥18 y) had DC with fixed flexion deformity of 20° or greater of the MCP or PIP joints in at least 1 finger. Joints were randomized in a 2:1 ratio to receive 10,000 U of collagenase (Auxilium Pharmaceuticals Inc., Malvern, PA) or placebo. Primary and, when possible, secondary and tertiary joints were identified for each patient. Patients could receive a maximum of 3 injections in the primary joint at 4- to 6-week intervals. Follow-up visits occurred at 1, 7, 14, and 30 days after each injection. Additional follow-up visits were scheduled at 2, 3, 6, 9, and 12 months from the last injection. Patients who achieved complete correction after the first injection could receive up to 2 additional injections in a secondary or tertiary joint; patients were re-randomized before receiving treatment in a secondary or tertiary joint. Patients with incomplete success or treatment failure after completing the double-blind phase or who desired treatment for other contractures were included in the open-label extension. In the open-label extension, patients could have up to 3 injections in a single joint (≥5 total injections per patient). Follow-up visits occurred at 1, 7, 14, and 30 days after each injection. All patients were splinted at night for an interval of 4 months after the last injection was administered.

In both the double-blind and the open-label treatment extension, the primary efficacy variable was *overall clinical success*, defined as a reduction in deformity to within 0° (normal) to 5° (flexion) of normal (0°) within 30 days of the last injection for the primary joint. Additional supportive efficacy variables included the time required to achieve success (correction to 0°–5° of normal) in the primary joint in the double-blind phase, and the number of injections required to achieve success. Recurrence, defined as a return of contracture (≥20°) in successfully treated joints, was evaluated. For all patients, follow-up visits occurred at 6, 9, and 12 months after the last injection and annually for 2 years after treatment. Additional follow-up evaluation on an annual basis is planned for 3 more years to accrue 5 years of follow-up data. Adverse events (AEs) were recorded during the study, including potential adverse immunologic effects.

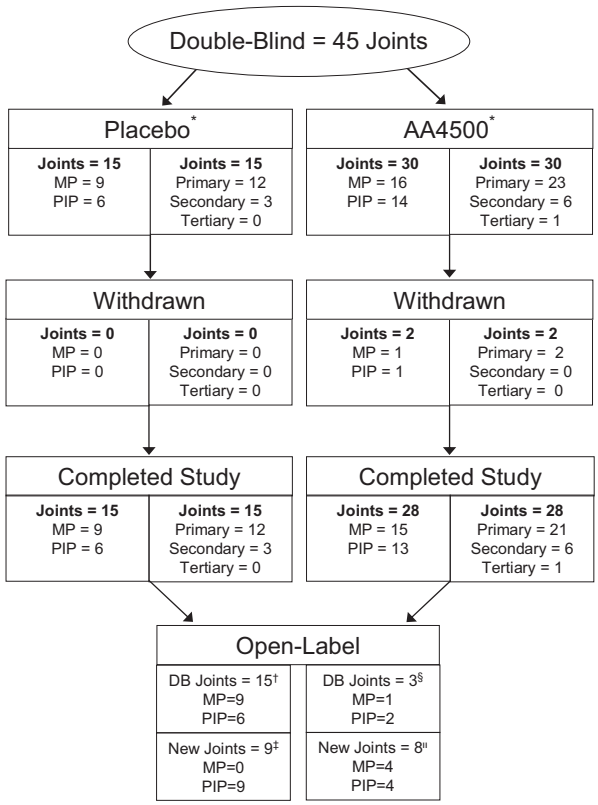
All statistical tests were 2-sided and differences were considered to be statistically significant at an α level of 0.05. Data are reported as the mean ± SD for continuous variables and as frequencies and percentages for categoric variables. The intent-to-treat sample, which included all randomized patients, was the primary population used for efficacy and baseline characteristics data analysis. Data that were missing for day 30 for the primary and secondary efficacy analyses were imputed using the last-observation-carried-forward method. The Kaplan-Meier method and the log-rank test, stratified by joint type, were used to determine the time to success and comparison of treatment groups. The safety population, defined as all patients who received at least 1 dose of study medication, was used for the analysis of safety data. The Fisher exact test was used to compare treatment groups experiencing AEs. AEs were tabulated according to preferred term, system organ class, severity, relationship to study drug, and seriousness. Adverse events leading to discontinuation of the study drug were recorded.

Results

Double-Blind Phase

Baseline demographics are shown in Table 1. All 35 patients were Caucasian and the majority (28 men and 7 women) were men. Thirty-three of the 35 patients randomized completed this phase. Patients were randomized by the joint to be treated (Fig. 1). Thus, for primary joint treatment, patients received up to 3 injections of either placebo only (12 patients [34%]) or active drug only (23 patients [66%]). Patients were re-randomized before receiving treatment for secondary and tertiary joints. Of 9 patients with secondary joint treatment, 6 patients (67%) received study drug and 3 patients (33%) received placebo. One tertiary joint was treated with study drug.

During this phase, 21 of 23 (91%) patients treated with the study drug versus 0 of 12 (0%) patients treated with placebo ($p < .001$) achieved clinical success with up to 3 injections in the primary joint for MCP and PIP contractures (Table 2). With a single injection of the study drug, 16 of 23 patients (70%) achieved clinical success; 2 of 23 (9%) patients achieved clinical success with 2 injections, and 3 of 23 (13%) patients achieved clinical success with 3 injections (Table 2). The mean number of injections for clinical success was 1.4.



DB=double-blind; MP=metacarpophalangeal; PIP=proximal interphalangeal.
*No joint received both placebo and AA4500 during DB study.
†Includes 1 joint for each of 3 patients who had 1 AA4500 and 1 placebo injection during the DB study.
‡Includes 1 joint for each of 2 patients who had 1 AA4500 and 1 placebo injection during the DB study.
§Does not include 1 joint for each of 3 patients who had 1 AA4500 and 1 placebo injection during the DB study.
||Does not include 1 joint for each of 2 patients who had 1 AA4500 and 1 placebo injection during the DB study.

Figure 1. Joint disposition.

For primary MCP joints, 12 of 14 (86%) achieved clinical success with up to 3 injections. For primary PIP joints, 9 of 9 (100%) achieved clinical success with up to 3 injections (Table 2). In the double-blind phase, a total of 30 joints (16 MCP, 14 PIP), including primary, secondary, and tertiary joints, were treated with collagenase. Twenty-two of 30 MCP and PIP joints (73%), 12 of 16 MCP joints (75%), and 10 of 14 PIP joints (71%) achieved clinical success after the first injection. By using a Kaplan-Meier analysis, the median time to clinical success for both MCP and PIP joints was 8 days ($p < .001$ vs placebo).

The most common AEs were local reactions to injections (Table 3). There were no reports of loss of sensation. Adverse events were mild to moderate in intensity and resolved within a mean of about 3 weeks. In regard to skin lacerations on cord rupture in 11 patients in both phases of the study, all healed by secondary intent. There were no infections and no skin grafts. Lacerations did not affect clinical outcome.

Open-Label Phase

Nineteen of the 33 patients who completed the double-blind phase entered the open-label phase. These patients included the 15 patients who received placebo on either the first or second joint randomized in the double-blind phase and the 4 patients who received active drug only but required further treatment.

All 19 patients with 35 involved joints (16 MCP, 19 PIP) were treated with collagenase (Fig. 1). Seventeen of 19 (89.5%) patients achieved clinical success in at least 1 treated joint; success rates were similar between patients with treated MCP versus

Table 2. Patients Achieving Clinical Success During Double-Blind Treatment

	Treatment Group				
	Collagenase		Placebo		P Value
	N	n (%)	N	n (%)	
Primary joint					
MCP and PIP					
First injection	23	16 (70)	12	0	<.001
Second injection	6	2 (33)	12	0	.047
Third injection	4	3 (75)	12	0	.002
Last injection	23	21 (91)	12	0	<.001
MCP					
First injection	14	10 (71)	7	0	.004
Second injection	3	1 (33)	7	0	.300
Third injection	2	1 (50)	7	0	.222
Last injection	14	12 (86)	7	0	<.001
PIP					
First injection	9	6 (67)	5	0	.031
Second injection	3	1 (33)	5	0	.375
Third injection	2	2 (100)	5	0	.048
Last injection	9	9 (100)	5	0	<.001
Secondary joint					
MCP and PIP					
First injection	6	5 (83)	3	0	.035
Last injection	6	5 (83)	3	0	.035
MCP					
First injection	2	2 (100)	2	0	.333
Last injection	2	2 (100)	2	0	.333
PIP					
First injection	4	3 (75)	1	0	.400
Last injection	4	3 (75)	1	0	.400
Tertiary joint (first injection)					
MCP and PIP	1	1 (100)	0	0	NA
MCP	0	0	0	0	NA
PIP	1	1 (100)	0	0	NA

P values for MCP and PIP joints are for comparisons between treatment groups from the Cochran-Mantel-Haenszel test stratified by joint type.
NA, not applicable.

Table 3. Selected Treatment-Related AEs and Time to Resolution During Double-Blind Phase

	Injection #1 (n = 23)		Injection #2 (n = 12)		Injection #3 (n = 6)	
AE	n (%)	d*	n (%)	d*	n (%)	d*
Collagenase treatment						
Injection site pain	23 (100)	11.8 ± 10.3	12 (100)	15.0 ± 13.9	6 (100)	11.3 ± 5.9
Edema (finger/hand)	23 (100)	8.3 ± 7.6	12 (100)	7.2 ± 3.9	6 (100)	4.7 ± 1.9
Ecchymosis (dorsal/volar)	10 (43)	6.2 ± 2.4	6 (50)	7.8 ± 4.0	2 (33)	15.5 ± 7.8
Skin laceration (at cord rupture)	3 (13)	13.0 ± 10.4	0	NA	0	NA
Lymphadenopathy (axillary/elbow)	9 (39)	6.2 ± 5.1	5 (42)	4.6 ± 3.6	1 (17)	2.0
Pruritus (hand/finger)	1 (4)	1.0	5 (42)	3.4 ± 4.2	3 (50)	2.0 ± 1.7
Blood blister	9 (39)	19.9 ± 10.9	2 (17)	7.5 ± 3.5	0	NA
Patients with ≥1 AE	23 (100)		12 (100)		6 (100)	
	(n = 12)		(n = 15)		(n = 15)	
Placebo treatment						
Injection site pain	6 (50)	2.0 ± 1.1	3 (20)	1.0 ± 1.0	1 (7)	2.0
Edema (finger/hand)	1 (8)	1.0	0	NA	0	NA
Ecchymosis (dorsal/volar)	0	NA	0	NA	0	NA
Skin laceration (at cord rupture)	0	NA	0	NA	NA	NA
Lymphadenopathy (axillary/elbow)	0	NA	0	NA	0	NA
Pruritus (hand/finger)	0	NA	0	NA	0	NA
Blood blister	0	NA	0	NA	0	NA
Patients with ≥1 AE	9 (75)		3 (20)		1 (7)	

NA, not applicable.
*Mean ± SD days to resolution = resolution date − onset date. Events that began and ended on the same day are counted as 0 days in duration.

PIP joints (Table 4). All 8 patients with 1 treated joint achieved clinical success. Of 7 patients with 2 treated joints, 5 patients achieved normalization in at least 1 of the 2 joints. Among patients with 3 treated joints, 2 patients achieved normalization in all 3 joints, and 1 patient achieved normalization in 1 of the 3 treated joints. One patient with bilateral disease with 4 treated joints achieved clinical success in all 4 joints of 1 hand and 2 joints of the other hand (Fig. 2). Of 35 joints treated, 27 joints (77%) achieved clinical success.

For MCP and PIP joint contractures, a single injection resulted in a 66% clinical success rate (Table 5). A total of 48 injections were required for success in 35 treated joints (16 MCP, 19 PIP), with a mean of 1.4 injections per joint. The mean number of injections was 1.5 for MCP joints and 1.3 for PIP joints. By using a Kaplan-Meier analysis, the time to clinical success ranged from 1 to 29 days and was not prolonged for second and third joints (Table 6).

Overall, during the controlled and open-label phases of the study, 62 joints (31 MCP, 31 PIP) were treated in 35 patients; 54 (87%) joints (90% MCP, 84% PIP) were clinical successes. All of the 54 successfully treated joints were followed up for 12 months, and 27 (50%) were followed up for 24 months. Over the 24-month follow-up period after the last injection, 4 PIP and 1 MCP joint had a recurrence. For the 4 PIP joints, the severity of recurrence was 30° at less than 12 months, 20° and 30° at 12 months, and 40° at 24 months. The severity of recurrence for the 1 MCP joint was 30° at 24 months. Of the recurrences in the 4 male patients, all had a

Table 4. Number of Patients Achieving Clinical Success During Open-Label Treatment

	MCP + PIP		MCP		PIP	
	N	n (%)	N	n (%)	N	n (%)
Joint 1						
First injection	19	12 (63)	12	6 (50)	7	6 (86)
Last injection	19	16 (84)	12	10 (83)	7	6 (86)
Joint 2						
First injection	11	7 (64)	2	2 (100)	9	5 (56)
Last injection	11	7 (64)	2	2 (100)	9	5 (56)
Joint 3						
First injection	4	3 (75)	1	1 (100)	3	2 (67)
Last injection	4	3 (75)	1	1 (100)	3	2 (67)
Joint 4						
First injection	1	1 (100)	1	1 (100)	NA	NA
Last injection	1	1 (100)	1	1 (100)	NA	NA
Global summary						
First injection	35	23 (66)	16	10 (63)	19	13 (68)
Last injection	35	27 (77)	16	14 (88)	19	13 (68)

NA, not applicable.

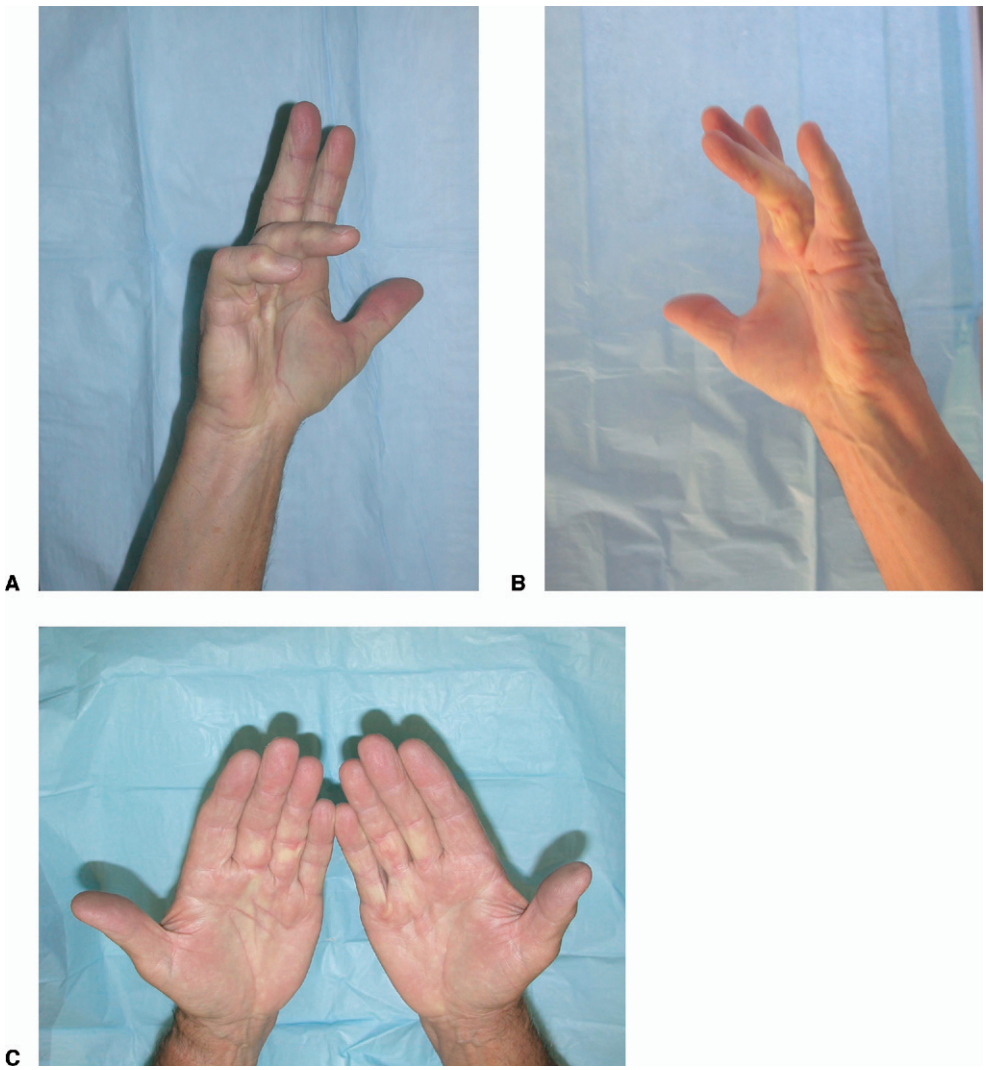


Figure 2. (A) A 70-year-old man with bilateral disease. Before treatment, contracture on the right small finger MCP was 20° and the PIP was 50°, the ring finger MCP was 50° and the PIP was 35°. (B) Same patient as in panel A before treatment, the left ring finger MCP was 35° and the left middle finger MCP was 30°. (C) Same patient as in panels A and B. This patient received 3 placebo injections in the blinded phase and the contractures did not respond. This patient entered the open-label phase and received 4 injections. All contractures were corrected to 0° and remain fully corrected at 2 years.

positive family history of DC. One female patient with a recurrence did not have a positive family history. There was no association of recurrences to ectopic disease.

Adverse events were of similar frequency, severity, and duration as in the double-blind phase (Table 7).

Table 5. Number of Joints Achieving Clinical Success During the Open-Label Phase

	MCP + PIP		MCP		PIP	
	N	n (%)	N	n (%)	N	n (%)
First injection	35	23 (66)	16	10 (63)	19	13 (68)
Last injection	35	27 (77)	16	14 (88)	19	13 (68)

Table 6. Time Required to Clinical Success in Open-Label Phase

	Median Number of Days to Clinical Success		
	MCP + PIP Joints	MCP Joints	PIP Joints
Joint 1	(n = 19) 8.0	(n = 12) 29.0	(n = 7) 8.0
Joint 2	(n = 11) 17.0	(n = 2) 19	(n = 9) 17.0
Joint 3	(n = 4) 4.5	(n = 1) 1.0	(n = 3) 8.0
Joint 4	(n = 1) 1.0	(n = 1) 1.0	0 NA

NA, not applicable.

Table 7. Selected Treatment-Related AEs and Time to Resolution During Open-Label Phase

AE	Injection #1 (n = 19)		Injection #2 (n = 12)		Injection #3 (n = 9)		Injection #4 (n = 5)		Injection #5 (n = 3)	
	n (%)	d*	n (%)	d*	n (%)	d*	n (%)	d*	n (%)	d*
Injection site pain	19 (100)	9.4 ± 5.3	12 (100)	8.8 ± 6.5	7 (78)	10.3 ± 9.1	3 (60)	8.7 ± 7.6	2 (67)	7.5 ± 3.5
Peripheral edema (hand)	19 (100)	5.2 ± 4.6	8 (67)	9.0 ± 7.2	6 (67)	4.5 ± 2.3	2 (40)	2 ± 0	2 (67)	4.5 ± 0.7
Ecchymosis (volar/ulnar)	14 (74)	13.5 ± 23.8	3 (25)	23.0 ± 20.0	2 (22)	6.5 ± 5.0	1 (20)	14.0	1 (33)	5
Skin laceration (at cord rupture)	5 (26)	11.8 ± 5.9	2 (17)	3.5 ± 0.7	1 (11)	9.0	0	NA	0	NA
Lymphadenopathy (axillary/elbow)	4 (21)	5.3 ± 4.4	0	0	0	0	0	NA	0	NA
Pruritus (hand/finger)	3 (16)	4.7 ± 4.5	2 (17)	2.5 ± 2.1	1 (11)	1.0	0	NA	0	NA
Blood blister	2 (10)	21.5 ± 0.7	1 (8)	7.0	0 (0)	0	0	NA	0	NA
Patients with ≥1 AE	19 (100)		12 (100)		7 (78)		3 (60)		2 (67)	

NA, not applicable.
*Mean ± SD days to resolution = resolution date − onset date. Events that began and ended on the same day are counted as 0 days in duration.

Patients who experienced an AE at the site of administration did not necessarily experience the same AE after repeated injections. Generally, AEs recurring in the same patient at subsequent injections did not change in severity. There were no adverse immune events.

Discussion

The epidemiology of DC has not been studied extensively but it appears to be more common in men than in women and to increase with age.[4,5,9] Age at onset in women, however, lags about 10 years behind age at onset in men, but at later ages it is equivalent in men and women.[4,5,9]

Dupuytren's contracture can result in hand deformity and impaired function. Dupuytren's contracture is slowly progressive and impaired hand function and deformity may become severe enough to interfere with activities of daily living, cause embarrassment, and consequently impact ability to work and quality of life. At present, surgery is the only effective treatment, but because recurrence is high, multiple corrective surgeries often are required. In addition, complications often occur after surgery; these include neurovascular bundle injury, hematomas, skin lesions, wound dehiscence, skin necrosis, infection, edema, joint stiffness, cold intolerance, pain, and reflex sympathetic dystrophy.[19,20] Thus, there is a need for other treatment options.

Various nonsurgical treatments evaluated for DC generally were found to be ineffective or not suitable for clinical use[16]; however, phase II studies with collagenase for DC have provided encouraging results.[17,18]

In this study we evaluated the long-term efficacy and tolerability of a mixed subtype collagenase and examined the recurrence rates in a phase III, double-blind study and its long-term, open-label extension. Collagenase safely and effectively restored normal finger extension in the majority of patients. A mean of 1.4 injections was required to normalize affected joints, and clinical success was achieved in 1 to 29 days. Of 62 joints treated, 54 (87%) were clinical successes during the placebo-controlled and open-label phases. Contracture recurrence was relatively low, occurring in 5 joints (1 MCP, 4 PIP), 1 before 12 months, 2 at 12 months, and 2 at 24 months after treatment. Recurrence did not occur until 6 months after successful joint treatment and recurrence severity ranged from 20° to 40°. A fasciectomy was performed by one of the authors (L.C.H.) on 2 patients, both for recurrence (1 MCP, 1 PIP joint). Another

surgeon in the practice also performed a fasciectomy for 1 patient for PIP joint recurrence. Pathology was consistent with Dupuytren's disease and was not altered by collagenase injections.

Many patients with PIP joint contractures have associated volar plate tightness and/or involvement of the spiral cords.[1–3] In the small number of patients with PIP joint contractures treated in this study, it was not entirely possible to delineate whether any of the patients had spiral cord involvement and how collagenase treatment may have alleviated long-standing joint contractures that often are resistant to surgical treatment. To the best of our knowledge, these patients may have had either central or abductor digiti minimi cords, which responded to collagenase lysis.

Adverse events were localized to the injection site, were generally of mild to moderate severity, and were transient in nature. In comparing the AEs in this study with the complication rates of surgery, our AEs were mild. McFarlane et al[14] reported on complications that occurred in a large series of 1,339 patients as follows: infection, 1.3%; hematoma, 2.2%; skin slough, 4.7%; loss of flexion, 4.6%; nerve injury, 1.5%; sympathetic dystrophy, 4.2%; arterial injury, 0.8%; gangrene, 0.1%; and other, 2.7%.

The data in this study are consistent with our earlier findings from phase II studies[17,18] and provide additional evidence confirming the effectiveness of collagenase as a nonsurgical treatment for DC. These data also suggest a low recurrence rate after collagenase treatment. Additional long-term studies of larger numbers of patients are warranted to verify the effectiveness and recurrence rate with collagenase treatment.

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References

1. Gudmundsson K. Eighteen years follow-up study of the clinical manifestations and progression of Dupuytren's disease. Scand J Rheumatol 2001;30:31–34.
2. Reilly R. A retrospective review of the management of Dupuytren's nodules. J Hand Surg 2005;30A:1014–1018.
3. Townley WA, Baker R, Sheppard N, Grobbelaar AO. Dupuytren's contracture unfolded. BMJ 2006;332:397–400.
4. Ross DC. Epidemiology of Dupuytren's disease. Hand Clin 1999;15:53–62.
5. Early P. Population studies in Dupuytren's contracture. J Bone Joint Surg 1962;44B:602–613.
6. Saboeiro AP, Porkorny JJ, Shehadi SI, Virgo KS, Johnson FE. Racial distribution of Dupuytren's disease in Department of Veterans Affairs patients. Plast Reconstr Surg 2000; 106:71–75.
7. Mikkelsen OA. Dupuytren's disease—a study of the pattern of distribution and stage of contracture in the hand. Hand 1976;8:265–271.
8. Rayan GM. Clinical presentation and types of Dupuytren's disease. Hand Clin 1999;15:87–96.
9. Gudmundsson KG, Arngrimsson R, Sigfusson N, Bjornsson A, Jonsson T. Epidemiology of Dupuytren's disease: clinical, serological, and social assessment. The Reykjavik Study. J Clin Epidemiol 2000;53:291–296.
10. van Rijssen AL, Werker PM. Percutaneous needle fasciotomy in Dupuytren's disease. J Hand Surg 2006;31B:498–501.
11. Makela EA, Jaroma H, Harju A, Anttila S, Vainio J. Dupuytren's contracture: the long-term results after day surgery. J Hand Surg 1991;16B:272–274.
12. Tonkin MA, Burke FD, Varian JP. The proximal interphalangeal joint in Dupuytren's disease. J Hand Surg 1985;10B: 358–364.
13. Rodrigo JJ, Niebauer JJ, Brown RL, Doyle JR. Treatment of Dupuytren's contracture. Long-term results after fasciotomy and fascial excision. J Bone Joint Surg 1976;58A:380–387.
14. McFarlane R, Botz J, Cheung H. Epidemiology of surgical patients. In: McFarlane R, McGrouther D, Flint M, eds. Dupuytren's disease. Edinburgh: Churchill Livingstone, 1990:201–238.
15. Bulstrode NW, Jemec B, Smith PJ. The complications of Dupuytren's contracture surgery. J Hand Surg 2005;30A: 1021–1025.
16. Hurst LC, Badalamente MA. Nonoperative treatment of Dupuytren's disease. Hand Clin 1999;15:97–107.
17. Badalamente MA, Hurst LC. Enzyme injection as nonsurgical treatment of Dupuytren's disease. J Hand Surg 2000; 25A:629–636.
18. Badalamente MA, Hurst LC, Hentz VR. Collagen as a clinical target: nonoperative treatment of Dupuytren's disease. J Hand Surg 2002;27A:788–798.
19. Tubiana R, Leclercq C, Hurst L, Badalamente M, Mackin E. Dupuytren's disease. London: Martin Dunitz Ltd., 2000:321.
20. Au-Yong IT, Wildin CJ, Dias JJ, Page RE. A review of common practice in Dupuytren surgery. Tech Hand Upper Extrem Surg 2005;9:178–187.