Efficacy and Safety of Collagenase Clostridium Histolyticum Injection for Dupuytren Contracture: Short-Term Results From 2 Open-Label Studies

Jörg Witthaut, MD, Graeme Jones, MD, Nebojsa Skrepnik, MD, PhD, Harvey Kushner, PhD, Anthony Houston, MD, Tommy R. Lindau, MD, PhD

Purpose The JOINT I (United States) and JOINT II (Australia and Europe) studies evaluated the efficacy and safety of collagenase clostridium histolyticum (CCH) injection for the treatment of Dupuytren contracture.

Methods Both studies used identical open-label protocols. Patients with fixed-flexion contractures of metacarpophalangeal (MCP) (20° to 100°) or proximal interphalangeal (PIP) joints (20° to 80°) could receive up to three 0.58-mg CCH injections per cord (up to 5 total injections per patient). We performed standardized finger extension procedures to disrupt injected cords the next day, with follow-up 1, 2, 6, and 9 months thereafter. The primary end point (clinical success) was reduction in contracture to within 0° to 5° of full extension 30 days after the last injection. Clinical improvement was defined as 50% or more reduction from baseline contracture.

Results Dupuytren cords affecting 879 joints (531 MCP and 348 PIP) in 587 patients were administered CCH injections at 14 U.S. and 20 Australian/European sites, with similar outcomes in both studies. Clinical success was achieved in 497 (57%) of treated joints using 1.2 ± 0.5 (mean ± SD) CCH injections per cord. More MCP than PIP joints achieved clinical success (70% and 37%, respectively) or clinical improvement (89% and 58%, respectively). Less severely contracted joints responded better than those more severely contracted. Mean change in contracture was 55° for MCP joints and 25° for PIP joints. With average contracture reductions of 73% and improvements in range of motion by 30°, most patients (92%) were "very satisfied" (71%) or "quite satisfied" (21%) with treatment.

From the Department of Hand Surgery, Uppsala University Hospital, Uppsala, Sweden; the Menzies Research Institute Tasmania, Hobart, Tasmania, Australia; the Tucson Orthopaedic Research Center, Tucson, AZ; the Department of Biostatistics, Auxilium Pharmaceuticals, Inc., Malvern, PA; the Caboolture Clinical Research Centre, Caboolture, Queensland, Australia; and the Pulvertaft Hand Centre, Kings Treatment Centre, Royal Derby Hospital, Derby, UK.

The authors also thank Kathryn J. Lucchesi, PhD, and Sherri D. Jones, PharmD, of MedVal Scientific Information Services, LLC, for providing medical writing and editorial assistance. The manuscript was prepared according to the International Society for Medical Publication Professionals' *Good Publication Practice for Communicating Company-Sponsored Medical Research: The GPP2 Guidelines*.

The authors thank the JOINT I investigators: Brian Bear, MD (Rockford Orthopedic Associates, Ltd., Rockford, IL); William DeVries, MD (Alpha Clinical Research, Clarksville, TN); F. Thomas D. Kaplan, MD (Indiana Hand Center, Indianapolis, IN); Charles Layman, MD (St. Vincent Medical Center, Portland, OR); John Lubahn, MD (Hamot Center for Clinical Research, Erie, PA); David Mandel, MD (David R. Mandel, MD, Inc., Mayfield Village, OH); J. Mark Melhorn, MD (PriVia, Wichita, KS); Nash Naam, MD (Southern Illinois Hand Center, Effingham, IL); Samuel Pegram, MD (Rheumatic Disease Clinic of Houston, Houston, TX); Troy Pierce, MD (St. Alexius Medical Center, Bismarck, ND); Nebojsa Skrepnik, MD (Tucson Orthopaedic Institute, Tucson, AZ); Teresa Sligh, MD (Providence Clinical Research, Burbank, CA); Philip Waller, MD (Accurate Clinical Research, Houston, TX); and Jon Zoltan, MD (Hope Research Institute, Phoenix, AZ); as well as the JOINT II investigators: Chris Bainbridge, MBBS (Pulvertaft Hand Centre, Derby, UK); Dean Boyce, MBBS (Morriston Hospital, Swansea, UK); Rick Milner, MD (Royal Victoria Infirmary, Newcastle, UK); Markku Harkonen, MD (Koskiklinikka, Tampere, Finland); Jarkko Vasenius, MD (Dextra, Helsinki, Finland); Stephan Wilbrand (Akademiska University Hospital, Uppsala, Sweden); Lars Dahlin, MD (University Hospital Malmo, Malmo, Sweden); Michel Boeckstyns, MD (Gentofte Hospital, Copenhagen, Denmark); Allan Ibsen, MD (Rigshospitalet, Copenhagen, Denmark, at the time of the study; now at Sahlgrenska Hospital, Gothenburg, Sweden); Bent Lange, MD (Dronninglund Sygehus, Dornninglund, Denmark); Pietro Giovanoli (University Hospital of Zurich, Zurich, Switzerland); Georges Rappoport, MD (Centre Thermal, Yverdon-les-Bains, Switzerland); Richard Lawson, MD (Royal North Shore Hospital, St. Leonards, New South Wales, Australia); Stephen Hall, MBBS (Emeritus Research, Malvern, Victoria, Australia); Jeffrey Karrasch, MBBS (Peninsula Clinical Research, Kippa Ring, Queensland, Australia); Stephen Coleman, MBBS (RiverCity Hospital, Auchenflower, Queensland, Australia); David Gilpin, MBBS (RiverCity Hospital, Auchenflower, Queensland, Australia); Anthony Houston, MD (Caboolture Clinical Research Centre, Caboolture, Queensland, Australia); Graeme Jones, MBBS (Menzies Research Institute, Hobart, Tasmania, Australia); and Andrew Taylor, MBBS (Goatcher Clinical Research Unit, Royal Perth Hospital, Perth, Western Australia, Australia).

Received for publication February 6, 2012; accepted in revised form October 4, 2012.

Supported by Auxilium Pharmaceuticals, Inc. J.W. is a member of Advisory Board Germany. H.K. was an employee of Auxilium at the time the study was conducted and the report was written.

Corresponding author: Jörg Witthaut, MD, Clinic for Hand Surgery, Schön Klinik Vogtareuth, Krankenhausstr. 20, D-83569 Vogtareuth, Germany; e-mail: jwitthaut@schoen-kliniken.de.

0363-5023/13/38A01-0002$36.00/0
http://dx.doi.org/10.1016/j.jhsa.2012.10.008

Physicians rated change from baseline as "very much improved" (47%) or "much improved" (35%). The CCH injections were well tolerated, causing no tendon ruptures or systemic reactions.

Conclusions Collagenase clostridium histolyticum was an effective, minimally invasive option for the treatment of Dupuytren contracture of a broad range of severities. Most treated joints (625 of 879) required a single injection. Treatment earlier in the course of disease provided improved outcomes. *(J Hand Surg 2013;38A:2–11. Copyright © 2013 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Therapeutic IV.

Key words Collagenase clostridium histolyticum, Dupuytren contracture, fixed flexion, nonsurgical, open label.

Dupuytren contracture is a disease of the hand characterized by an imbalance of collagen synthesis over degradation.[1–3] The etiology of Dupuytren contracture, though still controversial, is likely hereditary and either carried on an autosomal dominant gene or transmitted as a complex trait.[4] The prevalence of Dupuytren contracture ranges from 0.5% to 42.0% and varies with age, sex, geography, and ethnicity, occurring most commonly in older white men of northern European descent.[1,5] Prevalence estimates of Dupuytren contracture also vary with the stringency of the definition used to count cases.[5]

Firm soft tissue nodules develop in the palmar fascia of individuals with Dupuytren contracture because of myofibroblasts and fibronectin production.[1] These nodules may develop into collagen cords that contain an increased proportion of type III collagen relative to type I collagen[6] and connect the dermis to the palmar fascia, restricting normal joint extension.

Surgery to excise diseased cords has long been the most common treatment for Dupuytren contracture.[4] Although outcomes after surgical interventions are generally satisfactory, complications are relatively common (up to 39%) and can occur intraoperatively as well as postoperatively.[7,8] Postoperative hand therapy is typically required. Also, surgery may not always be appropriate, depending on a patient's age, comorbidities, or preferences.[7] Needle aponeurotomy, which involves using needles to puncture diseased cords,[8] is a less invasive option that is of renewed interest among hand surgeons. Nonsurgical options, including observation and radiation therapy for early Dupuytren lesions, have met with limited success.[9]

Collagenase clostridium histolyticum (CCH) (Xiaflex; Auxilium Pharmaceuticals, Inc., Malvern, PA) a purified mixture of 2 collagenases (AUX-I and AUX-II) from *C. histolyticum,* is approved in the United States[10] and Europe (as Xiapex; Pfizer Limited, Kent, UK)[11] for the treatment of adult patients with Dupuytren contracture who have a palpable cord. Able to cleave at multiple complementary sites, this mixture of collagenases is more efficient in cord disruption and collagen digestion than either collagenase alone.[12–17] Collagenase clostridium histolyticum preferentially cleaves fibrillar collagens (types I and III that characterize Dupuytren cords[18–20]), leaving intact globular collagens that make up the basement membranes of blood vessels and nerve cells (eg, type IV, type VI).[20,21]

The efficacy and safety of treatment with CCH has been demonstrated in clinical studies of patients with Dupuytren contracture, including data from 2 double-blind, placebo-controlled studies[22,23] and several observational studies.[17,24–26] The treatment algorithm in prior studies with CCH involved a maximum of 3 injections per cord (5–8 injections/patient) of 0.58 mg CCH.[22,23] Open-label extensions of several studies involved more injections with longer follow-up durations. In these studies, CCH consistently demonstrated superior efficacy over placebo in reducing contractures and increasing range of motion with minimal local adverse events (AEs).[22,23]

We conducted 2 concurrent 9-month, open-label studies (JOINT I and JOINT II) to evaluate the efficacy and safety of CCH (0.58 mg) used to reduce the degree of contracture in patients with advanced Dupuytren contracture.

MATERIALS AND METHODS

Study population

Patients of either sex, 18 years of age or older, were eligible for inclusion if they had advanced Dupuytren contracture with a fixed-flexion deformity ($\geq 20°$ and $\leq 100°$ measured by finger goniometry for metacarpophalangeal [MCP] joints and $\geq 20°$ and $\leq 80°$ for proximal interphalangeal [PIP] joints) in at least 1 fin-

ger other than the thumb that was caused by a palpable cord. We excluded patients if they had received treatment including surgery for Dupuytren contracture in the past 90 days; had other muscular, neurological, or neuromuscular disorders affecting the hands; had allergies to collagenase; were pregnant; had a history of stroke or bleeding or recent anticoagulant use; or had received doxycycline in the past 14 days.

Study design and procedures

Both studies had an identical open-label design and were conducted concurrently between September 2007 and December 2008. A total of 34 study centers participated, 14 of which were located in the United States (JOINT I) and 20 in Australia, the United Kingdom, Switzerland, Sweden, Denmark, and Finland (JOINT II). Study protocols conformed to the ethical guidelines of the Declaration of Helsinki as currently amended and were approved by duly constituted institutional review boards and ethics committees at the investigative sites before enrolling patients. We obtained written informed consent from each patient before any study procedures were performed. We registered JOINT I (NCT00528840) and JOINT II (ACTRN12607000217404) at http://www.clinicaltrials.gov and on the Australian New Zealand Clinical Trials Registry, respectively.

Patients could receive up to 5 CCH injections (5 treatment cycles) with a maximum of 3 per cord, separated by at least 30 days. Only 1 cord could be injected within a given treatment cycle. The investigator evaluated all MCP and PIP joints of all fingers (excluding the thumbs) of both hands and prioritized the joints to be treated. A treatment cycle consisted of one 0.58-mg CCH injection (in 0.25 mL diluent [0.9% sodium chloride/2 mmol/L calcium chloride] for MCP joints and 0.20 mL diluent for PIP joints), followed by efficacy and safety evaluations on days 1 (24 h postinjection), 7, and 30. Patients would undergo a standardized finger extension procedure (described below) to facilitate cord disruption on day 1 if a spontaneous disruption had not occurred.[22] The protocol did not recommend anesthetic use either at the time of CCH injection or during finger extension. Patients were fitted with a splint (its design was not specified in the protocol) and instructed to wear it at night for up to 4 months but otherwise to return to normal activities and perform finger flexion-extension exercises at home. The decision to reinject a cord that did not achieve correction to within 0° to 5° of normal was subject to patient or physician preference at day 30. Patients had additional follow-up visits on day 90, month 6, and month 9 for efficacy and safety evaluations.

Standardized finger extension technique

At 24 hours after injection, patients visited investigators' offices for follow-up as outpatients. Investigators performed standard passive extension at the first follow-up visit, applying moderate pressure to produce extension of the finger while patients' wrists were flexed. The force of extension was persistent and to the extent of patients' pain tolerance. Passive extension of the finger beyond patients' pain threshold was not advised. Finger extension was sustained for approximately 10 to 20 seconds. During manipulation of the PIP joint, the MCP joint was kept flexed. If the first extension attempt did not rupture the cord, second and third attempts could be performed, allowing an interval of 5 to 10 minutes between each manipulation. After 3 attempts, no further extension of the finger was performed. Obtaining complete rupture at the first return visit was helpful but not necessary. Direct pressure on the injection site was avoided because of tenderness.[22]

Efficacy and safety evaluation

The primary efficacy end point of the study was the proportion of joints achieving a reduction in contracture to within 0° to 5° of normal within 30 days of the last injection. We defined joints that achieved this end point as having achieved clinical success. Secondary end points included category of time to reach clinical success, percentage of joints achieving 50% or greater reduction from baseline contracture (defined as having achieved clinical improvement), percentage of decrease in degree of joint contracture from baseline to after the last CCH injection, and increase in range of motion (in degrees) between full-flexion and full-extension angles. We used standardized finger goniometry (neutral 0 method) to measure the angles of extension and flexion of all joints on the affected hand(s). We measured all extension angles with passive extension of the affected joint. Appropriately trained study personnel made finger goniometry measurements.

Physician and patient global assessments of disease severity (normal, mild, moderate, or severe) were evaluated at baseline. At the end of the study (month 9), physician assessment of improvement was graded on a 7-point Likert-type scale, where 1 = "very much improved" and 7 = "very much worse"; patient satisfaction was graded on a 5-point scale, where 1 = "very satisfied" and 5 = "very dissatisfied."

We evaluated the safety of CCH injections in patients who received at least 1 dose; safety data included AEs, clinical laboratory abnormalities, recurrence (when joint contracture increased to ≥20° with palpa-

TABLE 1. Demographics and Baseline Disease Characteristics and Severity

Characteristic	JOINT I Study (N = 201)	JOINT II Study (N = 386)	Total (N = 587)
Age (y)			
Mean (SD)	64.7 (9.9)	63.2 (9.6)	63.7 (9.7)
Range	39–87	35–86	35–87
Male (n [%])	164 (82)	334 (87)	498 (85)
Ethnicity (n [%])			
White, non-Hispanic	201 (100)	386 (100)	587 (100)
Hand with ≥ 1 contracture (n [%])[a]			
Left	66 (33)	106 (28)	172 (29)
Right	70 (35)	138 (36)	208 (36)
Both	65 (32)	140 (36.5)	205 (35)
Total contracture index (mean [SD])[b]	132.5 (109.8)	136.5 (104.2)	135.1 (106.0)
Affected joints per patient (n)[a]			
Mean (SD)	2.8 (2.0)	2.7 (1.9)	2.8 (2.0)
Range	1–11	0–13	0–13
Affected joints per affected hand (n)[a]			
Mean (SD)	2.0 (1.1)	2.0 (1.0)	2.0 (1.1)
Range	1–6	1–6	1–6
Affected MCP joints per patient (n)[a]			
Mean (SD)	1.5 (1.3)	1.5 (1.4)	1.5 (1.3)
Range	0–7	0–8	0–8
Affected PIP joints per patient (n)[a]			
Mean (SD)	1.3 (1.4)	1.2 (1.2)	1.2 (1.3)
Range	0–7	0–6	0–7
Family history of Dupuytren contracture (n [%])	80 (40)	165 (43)	245 (42)
History of risk factors and associated conditions (n [%])			
Vibration exposure	27 (13)	102 (26)	129 (22)
Hand trauma	30 (15)	64 (17)	94 (16)
Knuckle pads	3 (1)	2 (1)	5 (1)
Peyronie disease	3 (1)	10 (3)	13 (2)
Ledderhose disease	4 (2)	14 (4)	18 (3)
Diabetes	27 (13)	40 (10)	67 (11)
Epilepsy	4 (2)	9 (2)	13 (2)
Current alcohol use	124 (62)	339 (88)	463 (79)
Current tobacco use	31 (15)	64 (17)	95 (16)
Previous tobacco use	66 (33)	148 (38)	214 (36.5)
Age at diagnosis (y)			
Mean (SD)	55.4 (12.2)	52.1 (12.6)	53.2 (12.5)
Disease first detected by (n [%])			
Finger bending	86 (43)	172 (45)	258 (44)
Nodules	108 (54)	201 (52)	309 (53)
Pain	7 (3)	13 (3)	20 (3)
Duration of symptoms when medical treatment first sought (mo)			
Mean (SD)	63.5 (67.8)	62.2 (70.1)	62.6 (69.3)
Median (range)	36 (0–312)	36 (0–384)	36 (0–384)

(Continued)

TABLE 1. Demographics and Baseline Disease Characteristics and Severity (Continued)

Characteristic	JOINT I Study (N = 201)	JOINT II Study (N = 386)	Total (N = 587)
Prior treatment for Dupuytren contracture (n [%])			
None	125 (62)	217 (56)	342 (58)
Surgery[c]	62 (31)	162 (42)	224 (38)
Hand therapy	29 (15)	24 (6)	53 (9)
Injection	9 (4)	7 (2)	16 (3)
Other	9 (4)	6 (2)	15 (3)
Patient rating of disease severity at baseline (n [%])			
Mild	30 (15)	91 (24)	121 (21)
Moderate	99 (49)	200 (52)	299 (51)
Severe	72 (36)	95 (25)	167 (28)
Physician rating of disease severity (n [%])			
Mild	22 (11)	124 (32)	146 (25)
Moderate	121 (60)	181 (47)	302 (51)
Severe	58 (29)	81 (21)	139 (24)

[a]Number of joints at screening with fixed-flexion contractures 20° or greater caused by a Dupuytren cord; the mean number of affected joints was approximately evenly distributed between MCP and PIP.
[b]Sum of fixed-flexion contractures for all 16 joints (8 MCP and 8 PIP; all fingers excluding the thumbs) measured at screening.
[c]Fasciotomy, fasciectomy, and unspecified.

ble cord in patients who had previously achieved clinical success), and immunogenicity (antibodies to AUX-I and AUX-II).

Statistical analyses

We defined all primary and secondary end points *a priori* according to a statistical analysis plan. In addition, outcomes are presented by joint, and all results represent data pooled from both studies. For baseline pretreatment data, physician and patient global severity were correlated with the number of affected joints and total contracture index using Pearson r. Means (±SD) are presented for all numerically continuous data and percentages are presented for all categorical data, unless stated otherwise.

RESULTS

Baseline characteristics

Altogether, 587 of 679 screened patients enrolled in JOINT I and II. Demographic and baseline measures were similar (Table 1). Patient and physician global severity ratings of disease were highly correlated with each other ($r = 0.64$; $P < .001$) and with the number of affected joints and total contracture index ($P < .001$).

Treatment disposition

Overall, 879 joints were treated with 1,238 CCH injections. Mean injections per cord were 1.4 ± 0.7 (range, 1–4). More MCP cords (531; 60%) than PIP cords (348; 40%) were treated. More little finger (416; 47%) and ring finger (349; 40%) cords were treated than middle (84; 10%) and index finger (30; 3%) cords. One joint was treated in 62% of patients, 2 joints in 28%, 3 in 8%, and 4 to 5 in 2%.

Efficacy

Primary outcome: Clinical success was achieved in 497 of 879 treated joints (57%) (Fig. 1) and in 70% (369) of MCP and 37% (128) of PIP cords. The higher proportion of responding MCP versus PIP joints was consistent across both studies, as was the mean number of injections (1.2 ± 0.5) (Fig. 2). Of 879 joints treated, 625 (71%) did not require a second injection, and 780 (89%) did not require a third.

Of the 497 successfully treated joints, 292 (59%) responded within 7 days of the first injection (these joints were among the 625 that did not require a second injection). For MCP and PIP joint cords not achieving clinical success, 34 of 162 (21%) and 47 of 220 (21%) received the protocol-specified maximum 3 injections. For joints not achieving clinical success and not receiving the maximum 3 injections (128 MCP and 173 PIP joint), reasons included no palpable cord (MCP joint, 66 of 128, 52%; PIP joint, 76 of 173, 44%); injections in other cords reached the protocol-specified per-patient maximum of 5 per pa-

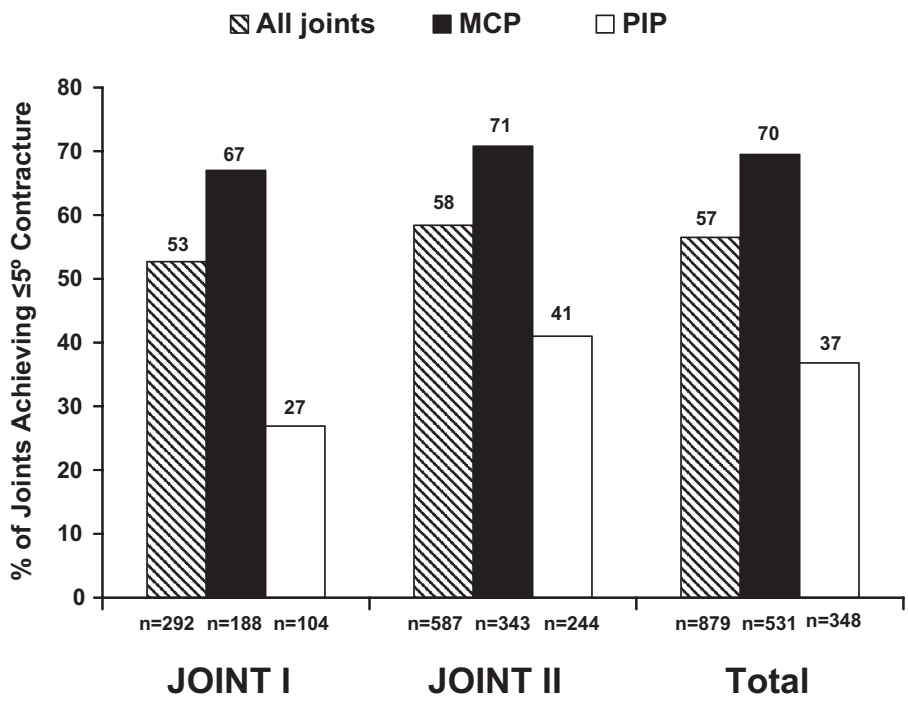

FIGURE 1: Primary end point: reduction in contracture to 5° or less within 30 days of last CCH injection. Numbers at the bottom indicate the number of joints treated.

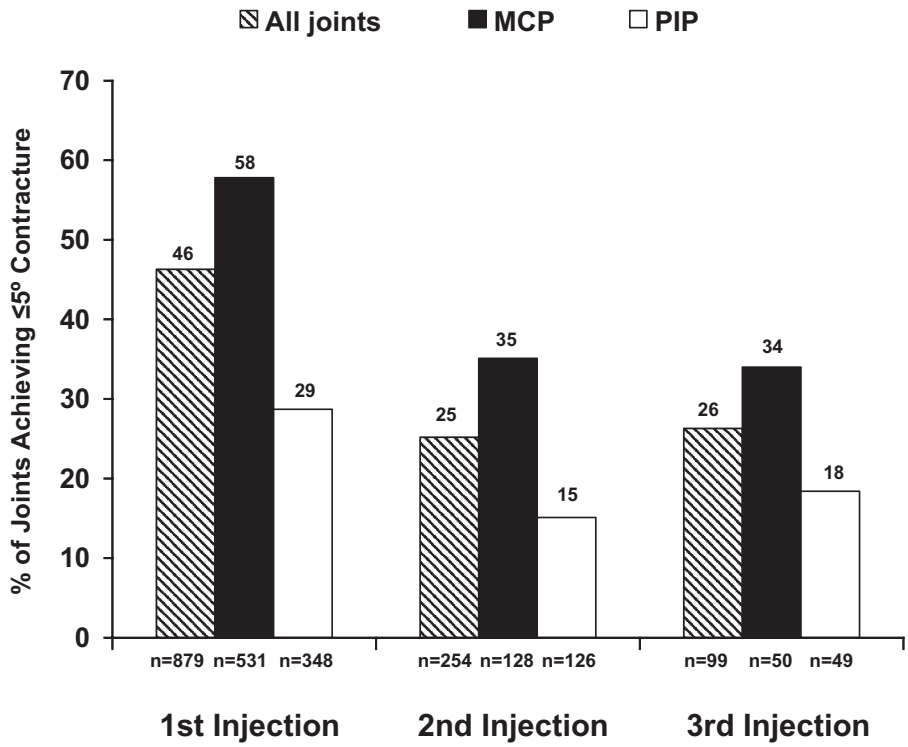

FIGURE 2: Reduction in contracture to 5° or less within 30 days after treatment following the first, second, and third CCH injections. Numbers below the bars indicate the number of joints treated that could be evaluated. Of the 879 joints treated, 625 (71%) did not receive a second injection and 780 (89%) did not receive a third injection.

TABLE 2. Secondary Outcome Measures: Clinical Success by Finger Injected, Clinical Improvement, and Change in Range of Motion by Joint (30 d After Last Injection)

	JOINT I Study (N = 292)	JOINT II Study (N = 587)	Total (N = 879)
Clinical success by finger (n [%])[a]			
Little	65/134 (49)	145/282 (51)	210/416 (50)
Ring	70/114 (61)	152/235 (65)	222/349 (64)
Middle	14/34 (41)	31/50 (62)	45/84 (54)
Index	5/10 (50)	15/20 (75)	20/30 (67)
All joints			
Clinical improvement (n [%])[b]	209 (72)	463 (79)	672 (76)
Mean change in contracture from baseline (%)	66.8 ± 41	75.4 ± 32	72.6 ± 35
Mean change in ROM from baseline (°)[c]	28.2 ± 20	30.6 ± 17	29.8 ± 18
MCP joint			
Clinical improvement (n [%])[b]	161 (86)	309 (90)	470 (89)
Mean change in contracture from baseline (%)	81.7 ± 28	85.2 ± 23	84.0 ± 25
Mean change in ROM from baseline (°)[c]	33.3 ± 17	32.9 ± 16	33.0 ± 17
PIP joint			
Clinical improvement (n [%])[b]	48 (47)	154 (63)	202 (58)
Mean change in contracture from baseline (%)	40.0 ± 47	61.6 ± 37	55.2 ± 41
Mean change in ROM from baseline (°)[c]	18.9 ± 22	27.5 ± 19	25.0 ± 20

ROM, range of motion. Mean percent change from baseline data is presented as ± SD.
[a]Primary end point (ie, reduction in contracture to 0° to 5° of normal within 30 d of last injection).
[b]Defined as a reduction in contracture of 50% or more from baseline.
[c]Defined as the difference between full-flexion and full-extension angles.

tient (MCP joint, 24 of 128, 19%; PIP point, 36 of 173, 21%); and satisfied with response (MCP joint, 10 of 128, 8%; PIP joint, 15 of 173, 9%).

Secondary outcomes: Secondary outcomes were similar in both studies (Table 2). After 1 injection, 609 of 879 joints overall (69%: 80% of MCP joints and 52% of PIP joints) achieved clinical improvement.

We pooled JOINT I and JOINT II data to evaluate clinical success by contracture severity. The MCP and PIP joints with lesser contracture severity (ie, ≤ 50° and ≤40°, respectively) showed a better response than more severely contracted joints (Fig. 3).

At the end of the study, 71% of patients were "very satisfied" and 21% "quite satisfied" with treatment; 47% of physicians rated change from baseline as "very much improved," and 35% as "much improved."

Safety

At least 1 AE was reported in 97% of patients. Most AEs were localized to the injection site and resolved without intervention within a median of 7 days (Table 3). Two patients had serious AEs that were possibly or probably related to study drug (deep vein thrombosis in the leg and tendonitis near the injection site). No tendon ruptures occurred.

Recurrence of contracture (≥ 20° contracture in successfully treated joints) occurred in 19 of 497 joints (4%).

Measured about 30 days after the first injection, most patients in the JOINT I and II studies had positive antibodies to AUX-I (93% and 92%, respectively) or AUX-II (85% and 89%, respectively). No AEs indicative of a major systemic immunological response to CCH were reported.

DISCUSSION

The JOINT I and II studies expand the efficacy and safety data available for CCH injections and provide results that are consistent with earlier studies.[17,22,24,25] Two randomized, placebo-controlled trials previously demonstrated significant positive efficacy outcomes associated with CCH, showing that cords injected with CCH were much more likely to achieve clinical success than those injected with placebo (CORD I, 64% vs 7%, $P < .001$; and CORD II, 44% vs 5%, $P < .001$).[22,23] The definition of clinical success (reduction of contracture to ≤ 5°) used throughout these studies is an objec-

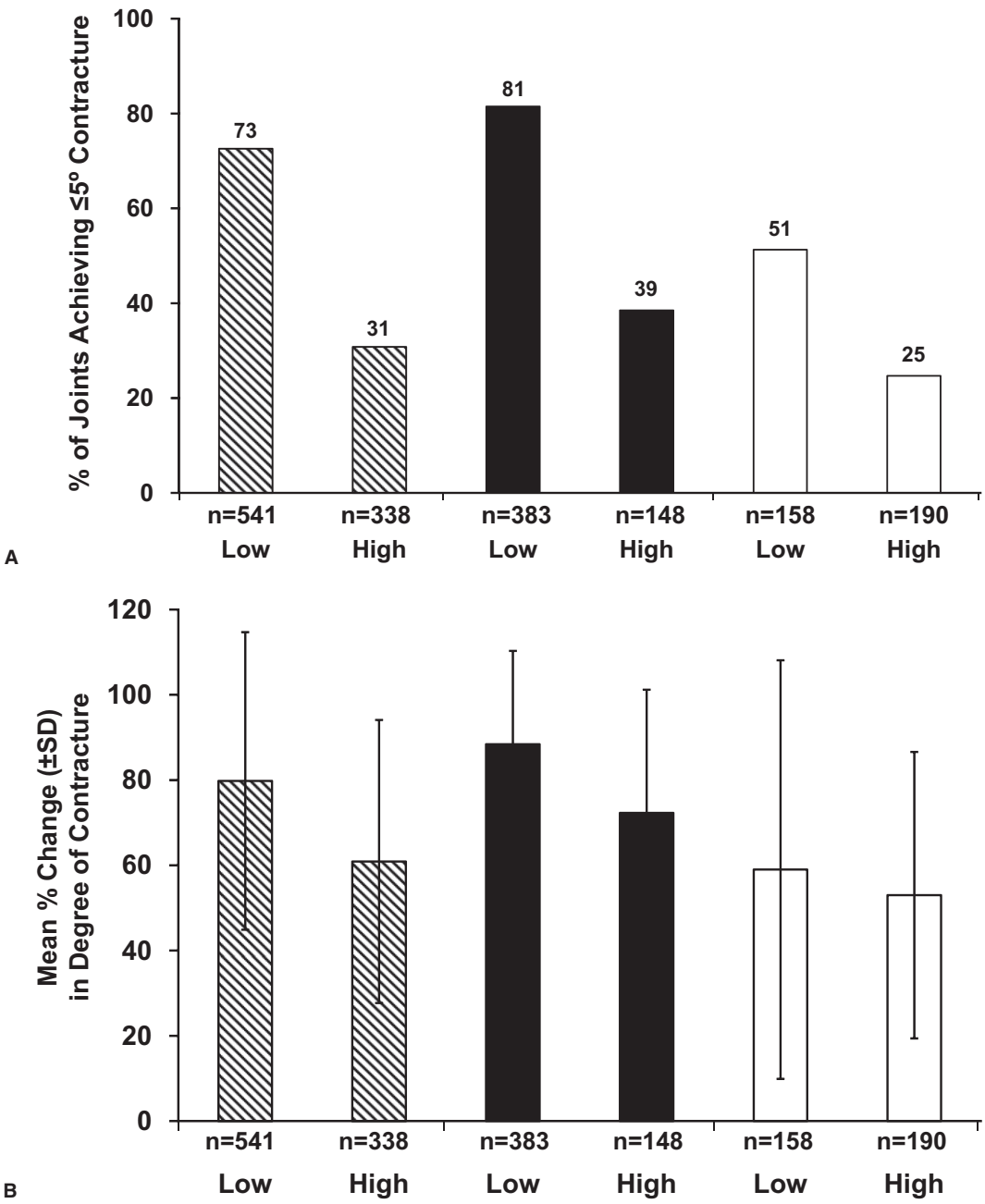

FIGURE 3: The JOINT I and JOINT II combined efficacy data, by joint type and baseline severity. **A** Reduction in contracture to 5° or less after last injection of CCH (percentages shown are treated joints that met primary endpoint). **B** Mean percent change in contracture from baseline to 30 days after last CCH injection (data shown are ± SD). n, number of joints treated with CCH; Low, joints with less severe contracture (≤ 50° for MCP joints and ≤ 40° for PIP joints); High, joints with more severe contracture (> 50° for MCP joints and > 40° for PIP joints).

tive and stringent measure of efficacy, setting a high standard not usually applied to other therapeutic interventions for Dupuytren contracture.[8,9,27] In the present studies, CCH resulted in clinical success or clinical improvement in most patients. Given the increasing popularity of needle aponeurotomy among hand surgeons as a less invasive, lower-cost alternative to other surgical options, the extent of correction achieved with CCH in these studies is generally comparable to results achieved with needle aponeurotomy.[8]

Individuals with less severe MCP and PIP joint contractures at baseline had better responses to CCH injections than those with more severe contractures. This is not surprising given that surgical outcomes also tend to produce better outcomes for primary disease and less severely contracted joints than for secondary disease

TABLE 3. Treatment-Related Adverse Events Occurring in 5% or More of Patients

Adverse Event	Total (N = 587)
Patients with ≥ 1 treatment-related AE (n [%])[a]	567 (97)
Edema peripheral (of treated extremity)	439 (75)
Contusion	350 (60)
Injection-site pain	248 (42)
Pain in extremity	224 (38)
Injection-site hemorrhage	216 (37)
Injection-site swelling	156 (27)
Tenderness	146 (25)
Pruritus	59 (10)
Skin laceration	55 (9)
Blood blister	48 (8)
Hematoma	45 (8)
Axillary pain	45 (8)
Lymphadenopathy	42 (7)
Ecchymosis	41 (7)
Injection-site vesicles	34 (6)

[a]All treatment-related adverse events to the end of the study.

and severe contractures. For example, 1 recent review summarizing fasciectomy and fasciotomy outcomes by disease stage reported satisfactory postoperative results in 97%, 82%, 73%, and 59% of patients for stages I through IV, respectively.[8]

In the JOINT I and II studies, severely contracted PIP joint cords had lower success rates than both MCP joints and less severely contracted PIP joints. The observation that PIP joints are more resistant to full correction than MCP joints is also consistent with findings in other studies.[8] In a randomized study by van Rijssen and colleagues,[27] fasciectomies or aponeurotomies performed on MCP joints were much more successful than those on PIP joints, affirming that severe contractures in PIP joints are associated with a less favorable prognosis. In a comprehensive review, Rayan[1] reported that after excising the offending cord in severe and prolonged PIP joint contractures, residual contracture can be expected, especially when the deformity exceeds 60°.

Although CCH treatment provided clinical benefit in severely contracted MCP and PIP joint cords, our finding of greater benefit in joints with milder contracture suggests that CCH could result in better outcomes when joints are treated earlier in the course of disease. Dupuytren contracture is a progressive disease, and the current evidence indicates that providing treatment to Dupuytren contractures of lower severity is more likely to result in clinical success than watching and waiting for contractures to become more severe.

We achieved clinical success after 1 CCH injection in most patients, and treatment was rated as "very satisfactory" by patients and physicians. Most patients who had unsuccessful clinical outcomes did not receive a second injection of the 3 injections of CCH allotted per joint. Treated cords that were no longer palpable received no additional injections. Cords that received additional injections appeared to achieve additional clinical successes.

The 9-month follow-up period in these studies limits the ability to make conclusions regarding long-term outcomes, including the likelihood of recurrence. Patients who achieved clinical success had the option to enroll in a 5-year follow-up study, which included patients from these and other phase 3 studies.

Complications associated with surgical treatment occur frequently in patients with Dupuytren contracture, especially when the severity of contracture is high.[28–30] Overall complication rates after surgery are reported to be between 4% and 39%. The most common complications reported have been wound healing (23%), scar pain from incisions (17%), dysesthesia or paresthesia (13%), hypoesthesia (10%), flare reaction (10%), reflex sympathetic dystrophy or complex regional pain syndrome (6%), infection (2%), and hematoma (2%).[7] Hurst et al[22] noted that surgical complications may include injury to the tendon, nerve, or artery; loss of flexion or grip strength; complex regional pain syndrome; skin necrosis; and complications related to wound healing. Complication rates after reoperation are even greater.[7]

After administration and up to 9 months after CCH injections, AEs that occurred were mild and transient and most resolved without intervention within 14 days. This is especially noteworthy given that the JOINT I and II studies collected and reported AEs systematically. The ability to repeat CCH treatment is currently under investigation, but this may provide options to health care practitioners that are not available after surgical correction in which the number of reoperations is typically self-limited.

Thus, in the context of complications associated with surgery or the potential need for lengthy hand therapy or other medical interventions,[7] the clinical impact of having a minimally invasive option that effectively reduces contractures in most patients is substantial. Finally, patient satisfaction after treatment with CCH was

favorable and consistent with physicians' global assessments of response.

In this study, treatment with CCH was safe and effective for the treatment of Dupuytren contracture. Collagenase clostridium histolyticum is a minimally invasive treatment that was particularly more effective when administered to joints with less severe contracture. Although the study protocol allowed up to 3 injections of CCH per joint, most joints required only 1 injection. Joints that did not achieve clinical success and received additional injections achieved further improvement. Although joints with less severe contracture had better outcomes, responses in more severely contracted joints were satisfactory and also provided clinical benefit. Given that CCH can be administered in a physician's office and hand therapy is not required posttreatment, there may no longer be a cause to delay treatment for Dupuytren contracture until contractures become severe enough to prompt traditional surgical intervention. The improvement in contractures observed with CCH treatment may lead to improvement in functionality of the hand such that there may be no need for surgical intervention.

REFERENCES

1. Rayan GM. Dupuytren's disease: anatomy, pathology, presentation, and treatment. *J Bone Joint Surg Am*. 2007;89(1):189–198.
2. Shaw RB Jr, Chong AK, Zhang A, Hentz VR, Chang J. Dupuytren's disease: history, diagnosis, and treatment. *Plast Reconstr Surg*. 2007; 120(3):44e–54e.
3. Melling M, Karimian-Teherani D, Mostler S, Behnam M, Sobal G, Menzel EJ. Changes of biochemical and biomechanical properties in Dupuytren disease. *Arch Pathol Lab Med*. 2000;124(9):1275–1281.
4. Thomas A, Bayat A. The emerging role of *Clostridium histolyticum* collagenase in the treatment of Dupuytren disease. *Ther Clin Risk Manag*. 2010;(6):557–572.
5. DiBenedetti DB, Nguyen D, Zografos L, Ziemiecki R, Zhou X. Prevalence, incidence, and treatments of Dupuytren's disease in the United States: results from a population-based study. *Hand (N Y)*. 2011;6(2):149–158.
6. Brickley-Parsons D, Glimcher MJ, Smith RJ, Albin R, Adams JP. Biochemical changes in the collagen of the palmar fascia in patients with Dupuytren's disease. *J Bone Joint Surg Am*. 1981;63(5):787–797.
7. Denkler K. Surgical complications associated with fasciectomy for Dupuytren's disease: a 20-year review of the English literature. *Eplasty*. 2010;(10):116–133.
8. Crean SM, Gerber RA, Hellio Le Graverand MP, Boyd DM, Cappelleri JC. The efficacy and safety of fasciectomy and fasciotomy for Dupuytren's contracture in European patients: a structured review of published studies. *J Hand Surg Eur*. 2011;36(5):396–407.
9. Betz N, Ott OJ, Adamietz B, Sauer R, Fietkau R, Keilholz L. Radiotherapy in early-stage Dupuytren's contracture: long-term results after 13 years. *Strahlenther Onkol*. 2010;186(2):82–90.
10. Xiaflex (collagenase clostridium histolyticum) [prescribing information]. Malvern (PA): Auxilium Pharmaceuticals, Inc.; October 2010.
11. Summary of product characteristics: Xiapex 0.9 mg powder and solvent for solution for injection [prescribing information]. Kent, UK: Pfizer Limited; March 14, 2011.
12. Mookhtiar KA, Van Wart HE. *Clostridium histolyticum* collagenases: a new look at some old enzymes. *Matrix Suppl*. 1992;(1): 116–126.
13. Matsushita O, Okabe A. Clostridial hydrolytic enzymes degrading extracellular components. *Toxicon*. 2001;39(11):1769–1780.
14. Mallya SK, Mookhtiar KA, Van Wart HE. Kinetics of hydrolysis of type I, II, and III collagens by the class I and II *Clostridium histolyticum* collagenases. *J Protein Chem*. 1992;11(1):99–107.
15. French MF, Bhown A, Van Wart HE. Identification of *Clostridium histolyticum* collagenase hyperreactive sites in type I, II, and III collagens: lack of correlation with local triple helical stability. *J Protein Chem*. 1992;11(1):83–97.
16. Van Wart HE, Steinbrink DR. Complementary substrate specificities of class I and class II collagenases from *Clostridium histolyticum*. *Biochemistry*. 1985;24(23):6520–6526.
17. Badalamente MA, Hurst LC. Efficacy and safety of injectable mixed collagenase subtypes in the treatment of Dupuytren's contracture. *J Hand Surg Am*. 2007;32(6):767–774.
18. Matsushita O, Koide T, Kobayashi R, Nagata K, Okabe A. Substrate recognition by the collagen-binding domain of Clostridium histolyticum class I collagenase. *J Biol Chem*. 2001; 276(12):8761–8770.
19. French MF, Mookhtiar KA, Van Wart HE. Limited proteolysis of type I collagen at hyperreactive sites by class I and II *Clostridium histolyticum* collagenases: complementary digestion patterns. *Biochemistry*. 1987;26(3):681–687.
20. Miyoshi S, Nakazawa H, Kawata K, Tomochika K, Tobe K, Shinoda S. Characterization of the hemorrhagic reaction caused by *Vibrio vulnificus* metalloprotease, a member of the thermolysin family. *Infect Immun*. 1998;66(10):4851–4855.
21. Trueb B, Bornstein P. Characterization of the precursor form of type VI collagen. *J Biol Chem*. 1984;259(13):8597–8604.
22. Hurst LC, Badalamente MA, Hentz VR, Hotchkiss RN, Kaplan FT, Meals RA, et al. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med*. 2009;361(10):968–979.
23. Gilpin D, Coleman S, Hall S, Houston A, Karrasch J, Jones N. Injectable collagenase Clostridium histolyticum: a new nonsurgical treatment for Dupuytren's disease. *J Hand Surg Am*. 2010;35(12): 2027–2038.
24. Badalamente MA, Hurst LC. Enzyme injection as nonsurgical treatment of Dupuytren's disease. *J Hand Surg Am*. 2000;25(4):629–636.
25. Badalamente MA, Hurst LC, Hentz VR. Collagen as a clinical target: nonoperative treatment of Dupuytren's disease. *J Hand Surg Am*. 2002;27(5):788–798.
26. Watt AJ, Curtain CM, Hentz VR. Collagenase injection as nonsurgical treatment of Dupuytren's disease: 8-year follow-up. *J Hand Surg Am*. 2010;35(4):534–539.
27. van Rijssen AL, Gerbrandy FS, ter Linden H, Klip H, Werker PM. A comparison of the direct outcomes of percutaneous needle fasciotomy and limited fasciectomy for Dupuytren's disease: a 6-week follow-up study. *J Hand Surg Am*. 2006;31(5):717–725.
28. Misra A, Jain A, Ghazanfar R, Johnston T, Nanchahal J. Predicting the outcome of surgery for the proximal interphalangeal joint in Dupuytren's disease. *J Hand Surg Am*. 2007;32(2):240–245.
29. Dias JJ, Braybrooke J. Dupuytren's contracture: an audit of the outcomes of surgery. *J Hand Surg Br*. 2006;31(5):514–521.
30. Bulstrode NW, Jemec B, Smith PJ. The complications of Dupuytren's contracture surgery. *J Hand Surg Am*. 2005;30(5):1021–1025.