Dupuytren Contracture Recurrence Following Treatment With Collagenase Clostridium Histolyticum (CORDLESS [Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study]): 5-Year Data

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Purpose Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study was a 5-year noninterventional follow-up study to determine long-term efficacy and safety of collagenase clostridium histolyticum (CCH) treatment for Dupuytren contracture.

Methods Patients from previous CCH clinical studies were eligible. Enrolled patients were evaluated annually for contracture and safety at 2, 3, 4, and 5 years after their first injection (0.58 mg) of CCH. In successfully treated joints (≤ 5° contracture following CCH treatment), recurrence was defined as 20° or greater worsening (relative to day 30 after the last injection) with a palpable cord or any medical/surgical intervention to correct new/worsening contracture. A post hoc analysis was also conducted using a less stringent threshold (≥ 30° worsening) for comparison with criteria historically used to assess surgical treatment.

Results Of 950 eligible patients, 644 enrolled (1,081 treated joints). At year 5, 47% (291 of 623) of successfully treated joints had recurrence (≥ 20° worsening)—39% (178 of 451) of metacarpophalangeal and 66% (113 of 172) of proximal interphalangeal joints. At year 5, 32% (198 of 623) of successfully treated joints had 30° or greater worsening (metacarpophalangeal 26% [119 of 451] and proximal interphalangeal 46% [79 of 172] joints). Of 105 secondary interventions performed in the successfully treated joints, 47% (49 of 105) received fasciectomy, 30% (32 of 105) received additional CCH, and 23% (24 of 105) received other interventions. One mild adverse event was attributed to CCH treatment (skin atrophy [decreased ring finger circumference from thinning of Dupuytren tissue]). Antibodies to clostridial type I and/or II collagenase were found in 93% of patients, but over the 5 years of follow-up, this did not correspond to any reported clinical adverse events.

Conclusions Five years after successful CCH treatment, the overall recurrence rate of 47% was comparable with published recurrence rates after surgical treatments, with one reported long-term
treatment-related adverse event. Collagenase clostridium histolyticum injection proved to be an effective and safe treatment for Dupuytren contracture. For those receiving treatment during follow-up, both CCH and fasciectomy were elected options. (J Hand Surg Am. 2015; 40(8):1597—1605. Copyright © 2015 by the American Society for Surgery of the Hand. All rights reserved.)

**Type of study/level of evidence** Therapeutic II.

**Key words** Collagenase clostridium histolyticum, Dupuytren contracture, recurrence, safety.

**Dupuytren Contracture** is a connective tissue disorder characterized by the formation of palmar nodules that can progress to form ropelike collagen cords extending into the fingers. The metacarpophalangeal (MCP) joint, proximal interphalangeal (PIP) joint, or both may be affected. Over time, cords can shorten and the joints become permanently contracted, resulting in deformity and impaired hand function.

A recent population survey found that 7% of U.S. adults had symptoms or diagnosis of Dupuytren contracture, and more than a third of those affected reported their hand deformity interfered with daily activities.

Although contracture recurrence following surgical intervention is recognized, the reported frequency of recurrence varies greatly. Reported recurrence rates range from 12% to 73% for fasciectomy/aponeurectomy and from 33% to 100% for open or needle fasciectomy/aponeurotomy. Major causes for this wide variation are the lack of clarity in descriptions and/or wide variability in definitions of recurrence, making comparisons among studies difficult. In addition, the studies reported in review articles span many decades, many different surgical techniques, and many rehabilitation protocols.

One U.S. Food and Drug Administration—approved pharmacological option for treating Dupuytren contracture is currently available. Collagenase clostridium histolyticum (CCH; Xiaflex; Auxilium Pharmaceuticals, Inc., Chesterbrook, PA) is an enzymatic treatment approved for adults with Dupuytren contracture with a palpable cord. CCH is also approved by the European Medicines Agency (Xiaflex; Auxilium UK Limited, Windsor, UK), Swissmedic (Xiaflex; Medius AG, Mutenz, Switzerland), Health Canada (Xiaflex; Actelion Pharmaceuticals Canada, Laval, Canada), and Australia Therapeutic Goods Administration (Xiaflex; Actelion Pharmaceuticals Australia, Belrose, Australia). In 2 phase 3, randomized, controlled clinical trials of patients with severe Dupuytren contracture, 44% to 64% of CCH-injected cords (0.58 mg/injection; up to 3 injections/joint) met the defined primary end point of contracture reduction to 5° or less within 30 days of the last injection, compared with 5% to 7% of placebo-injected cords (P < .001). Adverse events (AEs) with CCH were largely localized to the injection site and resolved within 1 to 4 weeks.

The risk of recurrence is critical in evaluating any treatment for Dupuytren contracture. The Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study (CORDLESS) was a prospective follow-up study for patients treated with CCH in previous clinical trials. The purpose of CORDLESS was to assess long-term recurrence and safety during 5 years following treatment with CCH for Dupuytren contracture. We recently reported interim 3-year results. At that time, of 623 joints that had previously demonstrated successful treatment (ie, ≤ 5° contracture), 35% (217 of 623) had a recurrence (≥ 20° increase with a palpable cord and/or secondary surgical/medical intervention). The recurrence rate was higher in PIP joints (56%) than in MCP joints (27%). Using a clinically accepted—and more often reported—but less stringent definition of 30° or greater increase, the 3-year recurrence rate was 22% (16% MCP and 38% PIP). In the first 3 years, no new long-term or serious adverse events (SAEs) were attributable to the prior CCH treatment. We report here final results from year 5 of CORDLESS.

**MATERIALS AND METHODS**

CORDLESS was a long-term, nontreatment, follow-up study conducted at 39 sites in the United States, United Kingdom, Denmark, Finland, Sweden, and Australia from 2009 through 2013. All patients were eligible to participate who had received 1 or more CCH injections and had 1 or more posttreatment assessment in previous clinical studies of CCH (9-mo open-label trials JOINT I and JOINT II; 3-mo double-blind trials Collagenase Option for the Reduction of Dupuytren’s (CORD) I and CORD II with 9-mo open-label extension). All sites had local or central institutional review board/ethics committee approval. Research was carried out in compliance with the Declaration of Helsinki as
Details of the study methods have been published. Briefly, enrolled patients were followed once annually for 4 years (years 2–5 after the first injection), with 6 months or longer between visits. At each visit, investigators (ie, treating physicians) examined and measured the MCP and PIP joints of each finger and determined change in contracture. Also obtained was a history of any AEs, hand surgeries, or CCH injection in the study of origin; (2) nondurability of response in joints that had been measurably improved (or greater, regardless of whether or not a palpable cord was present), or (2) a subsequent medical or surgical intervention involving the joint to correct a new or worsening contracture. (A joint with an increase of ≥20° in the contracture but no palpable cord was not assessed as having recurrence/nondurability/progression, nor was a joint with a palpable cord but an increase of <20°). The reference value for successfully treated joints was the measurement made at day 30 after the final injection, and the reference value for other joints was the lesser of the measurements made at day 30 or the last evaluation in the index phase 3 study.

**TABLE 1. Outcomes and Definitions**

<table>
<thead>
<tr>
<th>Joint Classification in Phase 3 Study of Origin</th>
<th>Outcome Measure in CORDLESS</th>
<th>Criteria in CORDLESS</th>
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<tbody>
<tr>
<td>Successfully treated (final contracture ≤ 5°)</td>
<td>Recurrence of contracture</td>
<td>(a) ≥ 20° increase in contracture compared with the reference value* + a palpable cord; OR (b) the joint underwent medical or surgical intervention primarily to correct new or worsening Dupuytren contracture in that joint</td>
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<tr>
<td>Measurably improved (≥ 20° reduction from pretreatment baseline, but final contracture &gt; 5°)</td>
<td>Nondurability of response</td>
<td>Same as above.</td>
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<tr>
<td>Not effectively treated (reduction of &lt; 20° from pretreatment baseline)</td>
<td>Progression of contracture</td>
<td>Same as above.</td>
</tr>
<tr>
<td>Responsive (successfully treated OR measurably improved)</td>
<td>Worsening of contracture</td>
<td>(a) ≥ 20° increase in contracture (or ≥ 30°, in posthoc analysis) compared with the reference value* ± palpable cord; OR (b) the joint underwent medical or surgical intervention primarily to correct a new or worsening Dupuytren contracture in that joint.</td>
</tr>
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*For successfully treated joints/recurrence, the reference value was the measurement at day 30 after the final injection in the index phase 3 study; for measurably improved joints/nondurability and for not effectively treated joints/progression, the reference value was the lesser of the measurement at day 30 or at the last evaluation in the index phase 3 study.
In historical clinical practice, contracture of 30° or greater has been commonly used as an indication for surgery (although surgery for lesser PIP joint contractures may be considered appropriate). Because successfully treated joints had posttreatment contractures of 5° or less (and, therefore, an increase in contracture of ≥ 30° would result in joints with ≥ 30° contractures), a post hoc analysis of worsening using a threshold of 30° or greater increase in contracture (± palpable cord) or medical/surgical intervention, was also performed. An increase of 30° or greater has been used previously by another group (van Rijssen et al14,15) to define recurrence.

### CCH dosing
In the previous clinical trials, patients could receive up to 3 injections of 0.58 mg CCH per cord (maximum of 8
injections per patient in the study). During CORDLESS, patients could receive CCH as part of ongoing treatment by their physician (CCH became commercially available in the United States in 2010, after the year 2 visits); however, this was not mandated by the protocol. Patients treated with CCH as an intervention while enrolled in CORDLESS were monitored for AEs at each annual visit.

**Statistical analyses**

Demographics, disease history, and characteristics of treated joints were summarized. Characteristics of the cohort of patients/joints assessed in CORDLESS were compared with those enrolled in the prior studies to ascertain that the CORDLESS cohort was representative of the overall population (test of proportions or a 1-sample t test for continuous variables). Nominal incidence rates of recurrence, progression, or worsening were calculated for all joints, by joint type, and by joint type/severity; AEs, SAEs, and the causal relationship of the AE/SAE to the phase 3 CCH injection were summarized. Immunogenic responses were evaluated as anti-AUX I and anti-AUX II titers over time.

**RESULTS**

Of 950 eligible patients from the original studies, 644 (68%) enrolled in CORDLESS and had 1 or more follow-up evaluations. Demographics and joint characteristics were similar for eligible and enrolled patient cohorts (Table 2). The 644 enrolled patients had 1,081 CCH-treated joints (648 MCP, 433 PIP); 623 had been successfully treated, 302 measurably improved, and 156 were not effectively treated (Fig. 1).

**Successfully treated joints**

The cumulative 5-year 20° or greater recurrence rate for successfully treated joints was 47% (291 of 623). The majority of recurrences (219 of 291; 75%) occurred prior to 3 years after treatment (Figs. 2 and 3).

Recurrence rates by joint type are shown in Figures 2 and 3. MCP joints of low baseline severity had a higher recurrence rate (41% [152 of 374]) compared with those of high severity (34% [26 of 77]). In contrast, low-severity PIP joints had a lower recurrence rate (63% [76 of 121]) than those of high severity (73% [37 of 51]). The mean contracture at year 5 for recurrent MCP joints (27°; n = 178) was less than pretreatment baseline (37°). Results were similar for recurrent PIP joints (n = 113) (year 5, 35°; baseline, 39°).

Using a clinically accepted threshold for surgery (≥ 30° contracture increase [± palpable cord] or medical/surgical intervention [post hoc analysis]), the rate of worsening was 32% (198 of 623) (MCP, 26% [119 of 451]; PIP, 46% [79 of 172]).
Measurably improved joints

Rates of nondurability of response in measurably improved joints are shown in Figure 2.

Responsive joints (successfully treated plus measurably improved)

Among responsive joints (n = 925), 48% (443 of 925) overall, 39% (234 of 603) of MCP joints, and 65% (209 of 322) of PIP joints had worsening (≥ 20° contracture increase [± palpable cord] or medical/surgical intervention). Using the threshold of 30° or greater increase, the rate of worsening was 35% (327 of 925) (MCP, 29% [174 of 603]; PIP, 48% [153 of 322]).

Joints not effectively treated

The rate of progression among joints that were not effectively treated was 52% (81 of 156) (MCP, 53% [24 of 45]; PIP, 51% [57 of 111]).

Medical/surgical interventions

By year 5, 16% (100 of 623) of successfully treated joints had a total of 105 medical/surgical interventions to correct worsened contractures. The most common were surgical fasciectomy (47% [49 of 105]) and CCH injection/segmental enzymatic degradation (30% [32 of 105]) (Fig. 4). Interventions were performed in 19% (56 of 302) of measurably improved joints (combined rate of 156 of 925 [17%] among responsive joints), and in 26% (40 of 156) of joints that were not effectively treated, for a total of 18% (196 of 1081) of all treated joints.

Safety

Collagenase clostridium histolyticum treatment was not part of CORDLESS. However, during the 5-year follow-up, 66 patients received commercially available CCH treatment for any joint at the discretion of treating physicians. Among these patients, 28 experienced AEs after injection of CCH. The most common (incidence, ≥ 10%) were edema peripheral (12%) and contusion (11%). Most AEs were mild to moderate; 1 (skin atrophy [decrease in ring finger circumference due to thinning of Dupuytren tissue]) was considered treatment-related by investigators. During CORDLESS, 103 patients experienced SAEs (none considered treatment-related), including 10 deaths. In year 5, 93% of patients were positive for anti-AUX I antibodies and 93% for anti-AUX II antibodies; these numbers did not correspond to any clinical AEs/SAEs reported.
DISCUSSION

The results of this study indicate that, for 53% of joints successfully treated with CCH (to $\leq 5^\circ$ residual contracture), the response was maintained for 5 years. Even among recurrent joints, the mean contracture was less than the mean baseline contracture. As with surgical treatment, recurrence was less common in successfully treated MCP joints (40%) than in PIP joints (66%). Successfully treated PIP joints were most likely to recur if they were severely contracted prior to CCH treatment. Further investigation is required to determine if earlier treatment of PIP joints has a longer-term effect. In contrast, higher recurrence rates were observed among MCP joints of lower severity; although consistent with interim results from year 3 of follow-up,\textsuperscript{11} this finding is somewhat counterintuitive. The rate of nondurability in measurably improved joints (60%) was slightly higher than the recurrence rate, indicating that joints that were more completely corrected with CCH injection initially were less likely to worsen over time.

Sixteen percent of successfully treated joints received further medical/surgical treatment over the 5-year course of follow-up. Although this percentage of retreatment appears to support a long-term response to CCH treatment, the lack of standardized indications for subsequent treatment limits our ability to draw any conclusions in this regard. CCH accounted for 30% of secondary interventions, second only to fasciectomy (47%). However, CCH was not approved by the U.S. Food and Drug Administration until after year 2 of the study; once approved, its use increased over time and it was the second most frequently (years 3 and 5) or most frequently reported (year 4) secondary intervention.

Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study used a conservative threshold ($\geq 20^\circ$ contracture increase) for \textit{a priori} definitions of recurrence. However, surgery has generally not been recommended until contracture is $30^\circ$ or greater, especially for MCP joints,\textsuperscript{1,13,16} and the threshold of $30^\circ$ or greater worsening to define recurrence has been used by others.\textsuperscript{14,15} Although our overall recurrence rate among successfully treated joints was 47%, 32% of successfully treated joints had worsening when a threshold of $30^\circ$ or greater increase in contracture (or medical intervention within 5 y after initial treatment) was used.

Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study evaluated recurrence specifically in joints that had previously achieved full correction (ie, $\leq 5^\circ$ contracture). Because surgical procedures such as fasciectomy typically achieve a short-term result of full correction, this would theoretically allow relevant comparisons between recurrence rates with CCH or surgery (ie, comparing long-term outcomes based on a common starting point). However, substantial variability in published descriptions and definitions of recurrence and reported recurrence rates throughout the twentieth century largely precludes meaningful comparisons of our results with those of historical surgical studies. van Rijssen and colleagues\textsuperscript{14,15} also established quantitative criteria for recurrence. They used an increase of total passive extension deficit of $30^\circ$ or greater compared with the 6-week follow-up values in previously treated joints. After 5 years, their recurrence rate following percutaneous needle fasciectomy (ie, a single procedure per cord) was 85% (45 of 53 treated hands); for limited fasciectomy, it was 21% (9 of 43 treated hands).\textsuperscript{15} In our study, 32% of joints successfully treated with CCH had $30^\circ$ or greater worsening during 5 years of follow-up; the rate of $30^\circ$ or greater worsening was slightly higher (35%) among the combined group of both successfully treated and measurably improved joints. In addition to their primary analysis, van Rijssen and colleagues\textsuperscript{14,15} also discussed outcomes among successfully treated joints in their study using criteria similar to those we used in CORDLESS. Successful treatment (with either limited fasciectomy or percutaneous needle fasciectomy) had been achieved in 132 (72%) MCP joints and 36 (34%) PIP joints; and among these successfully treated joints, 5-year recurrence rates following limited fasciectomy were 5% for both MCP (4 of 76) and PIP (1 of 19) joints. Following
percutaneous needle fasciotomy, they were 21% (12 of 55) for MCP joints and 24% (4 of 17) for PIP joints. However, the sample size was limited by a relatively low number of successfully treated joints, particularly for needle fasciotomy, and all patients were treated at a single site. A larger sample size from multiple study centers would be needed to fully understand the long-term efficacy of needle fasciotomy.

In CORDLESS, one third of all eligible patients failed to enroll, and 30% of those who did enroll withdrew over the course of follow-up. In some cases, patients may have been enrolled at sites that declined to participate in the follow-up study, possibly introducing site-specific bias. However, we did not detect any differences in patient or diseased joint characteristics between the eligible population and those who enrolled in CORDLESS, suggesting that the CORDLESS population was likely to be representative of the clinical study population as a whole. Finally, although it may be possible to use data from CORDLESS to identify factors associated with CCH were mild to moderate, local to the injection site, and transient.

In 1999, Tubiana identified 4 characteristics of successful treatment for Dupuytren contracture: to correct deformity, avoid complications, shorten postoperative recovery, and prophylactically prevent recurrences. Short-term placebo-controlled clinical trials have demonstrated the ability of CCH to meet the first 3 criteria. The results of CORDLESS, in which 53% of successfully treated joints had a durable response after 5 years of follow-up, address Tubiana’s final criterion. CCH is a viable nonsurgical option for safe and effective treatment of Dupuytren contracture with recurrence rates that are now better characterized.

ACKNOWLEDGMENTS

The authors also thank James P. Tursi, MD, Gregory J. Kaufman, MD, and Brian Cohen, PhD, for their contributions to this study, and Sherri D. Jones, PharmD, of MedVal Scientific Information Services, LLC, for providing medical writing and editorial assistance. This manuscript was prepared according to the International Society for Medical Publication Professionals’ Good Publication Practice for Communicating Company-Sponsored Medical Research: the GPP2 Guidelines.
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