SCIENTIFIC ARTICLE

Treatment of Recurrent Dupuytren Contracture in Joints Previously Effectively Treated With Collagenase *Clostridium histolyticum*

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Purpose Collagenase *Clostridium histolyticum* (CCH) is approved for the treatment of adults with Dupuytren contracture with a palpable cord. This open-label, phase 4 study evaluated the safety and efficacy of CCH for the retreatment of recurrent contractures in joints that were previously effectively treated with CCH.

Methods Patients participating in a long-term follow-up study who had contracture recurrence (increased $\geq 20^\circ$ with a palpable cord) after successful treatment in the previous study were eligible. Recurrent joint contractures were treated with up to 3 CCH injections ($\sim$ 1 month apart). Patients were followed for 1 year to evaluate safety. Assessments included change in joint contracture, range of motion, and the percentage of joints that achieved contracture of 5° or less at day 30 after the last injection.

Results The efficacy analysis included 51 patients with 1 treated joint per patient (31 metacarpophalangeal, 20 proximal interphalangeal). A total of 35 joints (69%) received 1 injection, 12 (24%) received 2 injections, and 4 (8%) received 3 injections. Fifty-seven percent of joints achieved contracture of 5° or less (29 of 51). Overall, 86% (43 of 50) patients had a 20° or greater increase in range of motion. The adverse event profile was consistent with previous studies. One ligament injury was reported.

Conclusions At a short-term follow-up of 1 year, recurrent contracture in joints previously successfully treated with CCH may be effectively retreated with up to 3 injections of CCH. *(J Hand Surg Am. 2017;■(■):1.e1-e8. Copyright © 2017 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Therapeutic IV.

Key words Dupuytren contracture, collagenase *Clostridium histolyticum*, recurrence.

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Dupuytren disease is a fibroproliferative disorder of the palmar fascia characterized by the formation of nodules, collagen cords, or both, in the palm leading to flexion contractures of the fingers.[1,2] Severe contractures can result in functional impairment that interferes with activities of daily living.[2,3]

Surgical options for treatment include extensive interventions such as fasciectomy and dermofasciectomy, as well as less-invasive techniques such as fasciotomy/aponeurotomy and needle aponeurotomy/percutaneous needle fasciotomy.[4,5] Generally, more-extensive procedures result in greater correction of the contracture relative to less-invasive procedures.[6]

Collagenase *Clostridium histolyticum* (CCH) is a minimally invasive treatment that is an alternative to some surgical interventions.[5–7] Collagenase *Clostridium histolyticum* is approved in the United States for the treatment of adults with Dupuytren contracture with a palpable cord. Concurrent treatment of up to 2 affected joints (total of 3 injections) may be performed in the same hand.[7] The beneficial outcomes of its use were observed in 2 phase 3 studies.[8,9] In these 2 placebo-controlled studies (CORD I[8] and CORD II[9]), rates of clinical success (ie, correction of contracture to 0°–5°) were significantly higher with CCH than with placebo.[8,9]

Recurrence of Dupuytren contracture presents a challenge regardless of the intervention used, although recurrence is generally more common either after less-extensive surgical procedures[4] or when a lesser degree of initial correction is achieved.[4,6] Available data on recurrence rates after specific interventions vary widely. In a systematic review of treatments for Dupuytren contracture (open partial fasciectomy, needle aponeurotomy, and collagenase injection), reported recurrence rates were similar after open partial fasciectomy and collagenase injection (12%–39%), but higher rates of recurrence were reported after needle aponeurotomy (50%–58%).[10] However, comparing recurrence rates among published studies is difficult because individual studies have surveyed different follow-up times and used a variety of definitions of recurrence.[10–12]

Treatment options for recurrent contractures after initial correction may include collagenase and surgery.[13] Published data on outcomes of surgical treatments specifically for recurrent contractures are somewhat limited.[14,15] Complications, such as digital nerve or digital artery injuries, may be more common with surgical interventions for recurrent contractures relative to initial treatment.[16]

Collagenase *Clostridium histolyticum* may be considered an appropriate treatment option for recurrent contractures in adults, provided there is a palpable cord to inject. Bainbridge and colleagues[17] analyzed data from phase 3 studies and found that the efficacy and safety of CCH treatment were similar regardless of whether patients previously had surgery to correct Dupuytren contracture on the hand with the CCH-treated joint. However, to date, no data have been published on the use of CCH for recurrence in joints previously treated with CCH. This study was conducted to assess the safety and efficacy of CCH in the retreatment of recurrent contractures in joints that were previously effectively treated with CCH.

MATERIALS AND METHODS

Study design and ethics

This open-label phase 4 study was conducted from March 2012 to October 2013 at 12 sites in the United States, Australia, and Europe (NCT01498640). The study protocol was approved by the local ethics committees, and research was carried out in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines. All participants provided written informed consent before the initiation of any study-specific procedures and were free to discontinue at any time.

Patients

Eligible patients were adult men and women with Dupuytren contracture who were participating in a long-term follow-up study (Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study [CORDLESS]), the eligibility criteria of which have been published previously.[18] To be eligible for the current study, patients from the CORDLESS study had to have at least 1 joint with the following: (1) effectively treated with CCH (contracture $\leq 5°$ at day 30 after the last CCH injection) in a previous phase 3 study (CORD I,[8] CORD II,[9] JOINT I,[19] or JOINT II[19]), (2) an increase in contracture of 20° or greater compared with the contracture at day 30 after the last CCH injection in that previous phase 3 study, and (3) a palpable cord. Patients were excluded if they were pregnant, lactating, or planned to become pregnant during the study, were hypersensitive to CCH, or were receiving, planned to receive, or had received anticoagulant medication within 7 days before CCH injection (except for $\leq$ 150 mg aspirin daily and nonprescription nonsteroidal anti-inflammatory drugs).

Treatments and study visits

A single recurrent joint was identified for retreatment at the enrollment visit. Joints were classified at baseline