Efficacy and Safety of Collagenase Clostridium Histolyticum in the Treatment of Proximal Interphalangeal Joints in Dupuytren Contracture: Combined Analysis of 4 Phase 3 Clinical Trials

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Purpose To examine the results of proximal interphalangeal (PIP) joint contractures from 4 phase 3 clinical trials of collagenase clostridium histolyticum (CCH) injection for Dupuytren contracture.

Methods Patients enrolled in Collagenase Option for Reduction of Dupuytren I/II and JOINT I/II with one or more PIP joint contractures (20° to 80°) received CCH 0.58 mg/0.20 mL or placebo (Collagenase Option for Reduction of Dupuytren I/II only) injected directly into a palpable cord. The percentage of PIP joints achieving clinical success (0° to 5° of full extension), clinical improvement (50% or more reduction in baseline contracture), and range of motion improvement at 30 days after the first and last CCH injections was assessed. The PIP joint contractures were classified into low (40° or less) and high (more than 40°) baseline severity. Adverse events were recorded.

Results A total of 506 adults (mean age, 63 ± 10 y; 80% male) received 1,165 CCH injections in 644 PIP joint cords (mean, 1.6 injections/cord). Most patients (60%) received 1 injection, with 24%, 16%, and 1% receiving 2, 3, and 4 injections, respectively. Clinical success and clinical improvement occurred in 27% and 49% of PIP joints after one injection and in 34% and 58% after the last injection. Patients with lower baseline severity showed greater improvement and response was comparable between fingers, as were improvements in range of motion. Adverse events occurring in more than 10% of patients were peripheral edema (58%), contusion (38%), injection site hemorrhage (23%), injection site pain (21%), injection site swelling (16%), and tenderness (13%). This incidence was consistent with data reported in phase 3 trials. Two tendon ruptures occurred. No further ruptures occurred after a modified injection technique was adopted.

Conclusions Collagenase clostridium histolyticum was effective and well tolerated in the short term in patients with Dupuytren PIP joint contractures. *(J Hand Surg Am. 2015;40(5):975–983.*

Type of study/level of evidence Therapeutic II.

Key words Collagenase clostridium histolyticum, Dupuytren contracture, nonsurgical treatment, proximal interphalangeal joint.

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Dupuytren contracture (DC) is a progressive fibroproliferative disorder affecting the palmar fascia of the hand. Pathologic collagen cords cause contracture of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints. Proximal interphalangeal joint contractures are considered more difficult to treat than MCP contractures and surgery is typically more challenging, particularly in advanced contractures that have an associated spiral cord.[1–4] Treatment is often complicated by shortening of the central slip and stiffness that develops in the PIP joint collateral ligaments and volar plate as a result of chronic PIP joint flexion.[1]

Whereas fasciectomy, dermofasciectomy, and fasciotomy are accepted treatments for DC, there is no definitive contracture threshold for surgical intervention.[5] Although progressive PIP joint contracture of 20° or more often is used as a benchmark, the decision to operate is based not only on the degree of contracture, but also on the level of functional disability and overall contracture progression over time.[3,5,6] It has been reported that the prognosis for achieving full extension without capsuloligamentous release in addition to fasciectomy lessens with prolonged PIP joint contracture.[7] Range of motion (ROM) improvement in PIP joints after fasciectomy is approximately 24° (50% contracture reduction)[8] and rates of postoperative complications range from 17% to 50%.[9] Limited fasciotomy has shown a cumulative complication incidence ranging from 4% to 39%.[10–12]

Collagenase clostridium histolyticum (CCH) is a nonsurgical enzymatic treatment approved by the United States Food and Drug Administration in 2010 for the treatment of adult patients with DC with a palpable cord. Collagenase clostridium histolyticum is injected directly into the cord, and approximately 24 hours later, after an optional local injectable anesthetic such as 1% lidocaine, standardized passive finger extension is performed to rupture the cord.[7,13] This minimally invasive treatment option can be performed in an office setting and requires little or no hand therapy. Adverse events (AEs) are generally localized to the injection site.[14,15] Risk of serious local adverse reactions include tendon rupture, pulley rupture, ligament injury, complex regional pain syndrome, and sensory abnormality of the hand. Therefore, care should be taken to avoid injecting into tendons, nerves, blood vessels, or other collagen-containing structures of the hand.[13]

We performed a combined analysis of patients enrolled in 4 randomized phase 3 clinical trials to evaluate the efficacy and safety of CCH in the treatment of PIP joint contractures. The clinical trials were: Collagenase Option for Reduction of Dupuytren (CORD) I (NCT 00533273),[15] CORD II (NCT00528840),[16] and JOINT I and II (NCT00528840 and ACTRN1260 7000217404), which were published together.[17]

MATERIALS AND METHODS

Inclusion/exclusion criteria

Adult patients enrolled in CORD I/II and JOINT I/II with DC in one or more PIP joints (20° or more and 80° or less contracture) were included in this analysis.[15–17] Exclusion criteria included any serious uncontrolled medical condition such as cancer, bleeding disorder, or recent stroke; and previous treatment of a target joint less than 90 days before, treatment with an investigational drug less than 30 days before, use of a tetracycline derivative less than 14 days before, or use of an anticoagulant drug (except 150 mg or less aspirin) less than 7 days before the first dose of CCH. Patients with a chronic muscular, neurologic, or neuromuscular disorder that affected the hands were excluded, as were those who had treatment for DC, including surgery, 90 days before the first dose of CCH, or who received any collagenase treatments less than 30 days before. A hand examination was performed for every joint treated, during which time the investigators selected joints suitable for CCH injections and excluded joints in which prior treatments, according to their assessment, might interfere with study results.

All studies were reviewed and approved by each individual center's institutional review board, and all patients provided written informed consent.[15–17] All study protocols conformed to the ethical guidelines of the Declaration of Helsinki as currently amended.[17] A total of 1,165 CCH injections were administered to 644 PIP joint cords in 506 patients with DC, mean age 63 ± 10 years (404 of 506 [80%] male).

Treatment

In CORD I and CORD II, patients were randomized to receive 0.58 mg CCH or placebo reconstituted and administered consistently with the prescribing information directly into the palpable cord. In the JOINT I/II open-label trials, patients received 0.58 mg CCH reconstituted in sterile diluent.[15–17] For a detailed description of the injection technique, see the CORD I Supplemental Appendix published online.[18]

Clinical end points

The PIP joints were classified into low (40° or less contracture) and high (more than 40° contracture) baseline severity.[15–17] The primary end point was clinical