

NONSURGICAL TREATMENT OF DUPUYTREN'S CONTRACTURE: FIRST-YEAR SAFETY RESULTS USING COLLAGENASE CLOSTRIDIUM HISTOLYTICUM

C.A. Peimer¹, G. Fiore², C. McGoldrick³

¹Marquette General Healthcare / College of Human Medicine / Michigan State University, Marquette, MI, USA;

²SSI Strategy, Westfield, NJ, USA; ³Auxilium Pharmaceuticals, Malvern, PA, USA

Disclosures: Auxilium Consultants (CAP, GF), Auxilium Employee (CM)

ABSTRACT

Introduction: Collagenase clostridium histolyticum (CCH) is FDA approved (February 2010) for treatment of adults with Dupuytren's contracture with palpable cord. CCH is injected directly into the cord. Followed ~24 hours later by a passive finger extension procedure that facilitates cord disruption and joint extension. In clinical trials (1082 patients; 2630 injections), 97.1% of patients receiving CCH experienced an adverse drug reaction (ADR). Most ADRs were localized to the injected extremity as follows: edema peripheral (77.4%), injection site swelling (24.1%), injection site pain (40.9%), ecchymosis/pain (39.2%), weakness (34.4%), erythema (17.9%), hematoma (34.2%), laceration (11.1%), injection-site pruritus (5.2%), pruritus (17.6%), lymphadenopathy (11.1%), axillary pain (6.7%). The majority of ADRs were mild to moderate in severity and resolved spontaneously. Other ADRs included 3 flexor tendon ruptures, 1 pulley injury, and 3 cases of local hypersensitivity reaction.

Objective: To summarize CCH adverse events (AEs) received by the marketing sponsor in the first 12 months post approval (~5400 doses).

Methods: A search of global safety data for CCH AEs received during the first 12 months after FDA approval identified 770 AEs in 115 patients (reporting rate: ~50 AEs/1000 doses). Reporting rates were used because incidence rates cannot be determined from voluntary post-marketing data.

Results: The AEs reported during the first post-marketing year were similar in type and severity to those reported in clinical trials and no safety related label changes were made. Skin laceration was the most commonly reported AE at 6.5/1000 doses, local edema at 5.6/1000 doses, and ecchymosis at 1.8/1000 doses. Skin lacerations occurred during the finger-extension procedure and typically healed without intervention; however, there were 2 reports that described skin grafting, three of the most important and costly treatment-related events were local hypersensitivity reaction (1 report), flexor tendon rupture (2 reports), and pulley injury (1 report). There were no reports of nerve injury thought to be related to CCH.

Conclusions: The post-marketing safety data received in the first year following product approval in the US suggests a similar safety profile compared with the profile established in five clinical trials. Local, non-serious reactions to treatment were the most frequent reports received. More serious, rare AEs, such as skin tears that required grafting and flexor tendon ruptures, are important to note and to understand fully to establish the important context.

INTRODUCTION

Dupuytren's disease is a fibroproliferative disorder in which collagen cords form, thicken, and shorten, causing permanent flexion contractures and possible deformity that impairs hand function.¹

Dupuytren's contracture has traditionally been treated using surgery (fasciectomy or fasciotomy); however, surgical procedures can be associated with prolonged postoperative morbidity and extensive hand therapy, as well as serious complications.^{2,3}

Collagenase clostridium histolyticum (CCH) is the first FDA-approved nonsurgical treatment for Dupuytren's contracture.

Two pivotal randomized, double-blind, placebo-controlled CCH clinical trials demonstrated overall reduction in contracture of the primary affected joint (metacarpophalangeal [MP] or proximal interphalangeal [PIP]) to 0°-5° in 64% and 44% of CCH-treated patients, respectively, compared with 7% and 5% of placebo-treated patients following up to 3 injection and finger-extension cycles.^{4,5} Serious complications following CCH administration were uncommon in these CCH clinical trials.

Among 1082 patients (2630 injections), a review of the adverse drug reactions (ADRs) deemed related to CCH treatment by study investigators in phase 2 and 3 clinical trials found that most ADRs were limited to the treated extremity, were mild to moderate in severity, and resolved spontaneously.⁶

The serious treatment-related ADRs in the trials included 3 flexor tendon ruptures, 1 flexor pulley injury, 1 complex regional pain syndrome, 1 case of tendonitis, and 1 finger deformity (boutonniere deformity).⁷

OBJECTIVE

To report the most common adverse events (AEs) for CCH that were received by the marketing sponsor during the first 12 months post FDA approval in the US.

METHODS

A search of safety data for AEs received by the CCH marketing sponsor (Auxilium Pharmaceuticals, Inc., Malvern, PA, USA) during the first 12 months after US approval, February 3, 2010, through February 2, 2011, was conducted.

Reporting rates are the number of spontaneous AE reports received by the marketing sponsor for the population at risk (i.e., patients treated/exposed to product: ~5400 doses in this period based on distribution records during this initial 1-year period).

Reporting rates were used because the incidence rate (the number of events/population at risk during a period of time) cannot be determined from US voluntary post-marketing data.

Three uncommon AE cases involving flexor tendon rupture and pulley/ligament injury are described.

DATA ANALYSIS

The most common AEs are described as the percentage of reports for the particular AE compared with the total number of AE reports received for CCH during the first year after US approval.

AEs that comprised >2% of the total post-marketing events received are presented, as are 3 clinically notable AE cases involving 2 flexor tendon ruptures and 1 flexor pulley/ligament injury.

RESULTS

Table 1. Most Commonly Reported Post-marketing AEs Following CCH Injection for Dupuytren's Contracture.

Number of Reported AEs	Post-marketing AEs (%)	Reporting Rate* per 1000 Doses
Skin tear (35)	13.0	6.5
Peripheral edema (30)	11.1	5.6
Contusion (26)	9.6	4.8
Drug ineffective (13)	4.8	2.4
Injection-site hematoma (10)	3.7	1.9
Lymphadenopathy (8)	3.0	1.5
Pain in extremity (8)	3.0	1.5
Blood blister (8)	3.0	1.5
Injection-site pain (7)	2.6	1.3
Tenderness (6)	2.2	1.1

*270 total AEs reported; [†]Approximately 5400 doses in the current analysis. AE = adverse event.

- A total of 270 AEs were reported in 115 patients.
- The AEs received during the first post-marketing year were similar in type and severity to those reported in the clinical trials.
- Four reports described localized hypersensitivity or allergic reaction involving extremity rash or pruritus; and none described systemic or anaphylactic reactions.
- A total of 35 skin tears were reported; and all skin tears occurred during the finger-extension procedure.
- Most skin tears healed without intervention; 2 patients received a skin graft.
- There were 2 reports of hypoaesthesia involving the CCH-treated hand; however, there were no reports of specific nerve injury.

Cases of Severe Adverse Events

Case 1. Flexor Tendon Rupture.

- 65-year-old man.
- CCH treatment for cord involving the PIP joint of the left little finger.
- At 2 weeks post-CCH injection, the fifth finger was straight but would not bend actively.
- Ultrasound confirmed profundus tendon rupture.
- Tendon graft procedure was scheduled for 1 month after the AE diagnosis.
- No additional follow-up information was reported.

Case 2. Flexor Tendon Rupture.

- 71-year-old man.
- CCH treatment for a 30° left ring finger MP cord. At ~3 months post-CCH injection, physical examination confirmed flexor digitorum superficialis rupture.
- No corrective procedures were planned or undertaken at the time of the report.

Case 3. Pulley/Ligament Injury Diagnosed by MRI.

- 52-year-old woman.
- CCH treatment for a cord of the right ring finger MP joint.
- Following the finger-extension procedure, she was unable to completely flex her MP joint (i.e., 50% decrease in active range of motion).
- MRI scan showed increased distance between the bone and flexor tendons, consistent with A2 pulley incompetence.
- The patient improved clinically, but could not completely flex the MP joint.
- No additional follow-up information was reported.

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CONCLUSIONS

Post-marketing safety data received by the CCH marketing sponsor in the first year following FDA approval and US launch showed a safety profile similar to that demonstrated in clinical trials.^{4,5}

No safety-related changes were made to the product label.

Local, non-serious effects from treatment were the most frequent reports received; no systemic allergic or anaphylactic reactions were reported.

One comprehensive review of major surgical and postoperative complications found an average of 15.7% (range 3.6%-39.1%) of patients having fasciectomy experienced major complications.¹

Rare AEs included 2 flexor tendon ruptures and 1 A2 pulley/ligament injury.

Serious AEs associated with CCH were reported infrequently (i.e., tendon rupture reporting rate was 0.37/1000 doses), and are less common than documented serious complications from surgical treatments.

One limitation of the current evaluation is that all of the AE and follow-up recovery or treatment information may not have been reported and available for analysis; however, we believe it unlikely that serious events were not reported.

For example, in Case 3, the biomechanical relationship between MRI-diagnosed A2 pulley incompetence and partial loss of MP flexion is not clear.

Reports received from post-marketing monitoring are valuable in that they play a critical role in the early identification of safety signals and the characterization of the safety profile of a drug, and are most likely to capture reports of serious post-treatment problems.⁸

Corresponding Author: Clayton A. Peimer.