Nonsurgical treatment of Dupuytren's contracture: 1-year US post-marketing safety data for collagenase clostridium histolyticum

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Abstract

Background Collagenase clostridium histolyticum (CCH) is a Food and Drug Administration-approved treatment for adult patients with Dupuytren's contracture with a palpable cord that has been shown efficacious and safe in clinical trials.

Methods This paper summarizes the most common post-marketing clinical adverse event (AE) reports received by the manufacturer of CCH and sponsor of the US Biologics License Application (Auxilium Pharmaceuticals, Malvern, PA, USA) during the first 12 months after drug approval and commercialization in the USA.

Results Of the 115 AE reports describing 270 AEs voluntarily received from patients or health care providers after approximately 5,400 injections of CCH administered, the most common AEs involved local, nonserious reactions to treatment, including skin tears, peripheral edema, and contusion. There were few serious AEs observed (0.6% reporting rate per 1,000 injections), and two flexor tendon ruptures and one flexor pulley injury were reported.

Conclusions Analysis of post-marketing AEs received for CCH in the first year post-approval supports the safety profile reported earlier during clinical development and did not reveal additional clinical risks or concerns about CCH.

Keywords Collagenase clostridium histolyticum · Dupuytren's contracture · Clinical adverse event

Introduction

Collagenase clostridium histolyticum (CCH) was approved in the USA by the Food and Drug Administration (FDA) (February 2010) for the treatment of adult patients with Dupuytren's contracture with a palpable cord. CCH is injected directly into a Dupuytren's cord affecting a proximal interphalangeal (PIP) or metacarpophalangeal (MP) joint. CCH contains a fixed-ratio mixture of two bacterial collagenases, a class I *Clostridium histolyticum* collagenase that lyses the terminal ends of the collagen molecule and a class II *C. histolyticum* collagenase that lyses internal sections of collagen [9]. The collagenases appear to work synergistically to digest and weaken the collagen cord, so that approximately 24 h after the injection, a passive finger extension procedure can be performed, if necessary, to facilitate cord disruption and restore joint extension [13]. Two pivotal randomized, double-blind, placebo-controlled CCH clinical trials demonstrated overall reduction in contracture of the primary joint (MP or PIP) 0° to 5° in 64 and 44% of CCH-treated patients, compared with 7 and 5% of placebo-treated patients following up to three injection and finger extension procedure cycles [10, 11].

Dupuytren's contracture, initially characterized by Sir Astley Cooper in the 1820s but named after Baron Guillaume Dupuytren following his description of the disease in

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1831, has traditionally been treated using surgery (fasciectomy or fasciotomy) since the 1800s [4, 5, 8, 12]. However, surgical procedures are associated with prolonged post-operative morbidity, necessitating extensive hand therapy as well as potentially serious complications, according to reports published throughout the twentieth century [3, 6]. Alternatively, CCH is the first FDA-approved nonsurgical treatment and hand therapy is not required. Serious complications following CCH administration were uncommon in the CCH clinical trials. Among 1,082 patients (2,630 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 [7]. The most common ADRs were localized to the injection area and included peripheral edema, contusion/ecchymosis, pain (injection site, extremity, axilla), localized bleeding, swelling, pruritus, skin tear during the manipulation procedure, and short-term regional lymphadenopathy. Across all phase 2 and phase 3 trials, there were no reported cases of systemic hypersensitivity reactions or anaphylaxis. The serious treatment-related ADRs in the clinical program included three flexor tendon ruptures, one flexor pulley injury, one complex regional pain syndrome, one case of tendonitis, and one finger deformity (boutonniere deformity) [2, 7].

This report discusses the most common post-marketing adverse events (AEs) for CCH that were received by the manufacturer during the first 12 months post-approval in the USA (approximately 5,400 injections). Three uncommon, but notable, post-marketing AE reports (two tendon ruptures and one flexor pulley injury) are described.

Methods

In the USA, safety data are received by FDA through the MedWatch program, which is a voluntary program wherein consumers and health care professionals may “report” to FDA when issues arise during use of products. FDA then enters information into its Adverse Event Reporting System database and uses the data to determine further actions.

By law in the USA, medical product marketing sponsors/manufacturers must also maintain a system for receiving and handling safety information for their products and for reviewing the information and sending to FDA, and others, as appropriate. Additionally, FDA sends some of the information it receives to manufacturers.

A search of safety data for AEs received by the CCH marketing sponsor (Auxilium Pharmaceuticals, 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 manufacturer for the population at risk (i.e., patients treated/exposed to the product; approximately 5,400 injections in the 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. 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, across all AE categories, during the period. AEs that comprised >2% of the total post-marketing events received by the manufacturer are presented, as are the uncommon, but clinically notable, three AE cases involving flexor tendon rupture and flexor pulley injury.

Results

A total of 270 AEs were reported in 115 patients. The majority of reports were submitted by physicians, with eight reports submitted by a patient or nonmedical person. The AEs received during the first post-marketing year were similar in type and severity to those reported in CCH clinical trials. Based on these data, no safety-related changes were made to the FDA-approved product label during the period. Of the 270 AEs received, 13% were skin tears, 11.1% were peripheral edema in the extremity, 9.6% were local contusion, and 4.8% reported that the drug was ineffective. Additional AEs representing >2% of the total post-marketing reported events are presented in Table 1, along with reporting rates by AE.

Among important and likely treatment-related AEs, four reports described hypersensitivity or allergic reaction

Table 1 Most commonly reported post-marketing adverse events following CCH injection for Dupuytren’s contracture

Number of reported adverse events	Post-marketing adverse events (%) ^a	Reporting rate ^b per 1,000 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

^a Two hundred seventy total adverse events reported

^b Approximately 5,400 injections in the current analysis

involving localized rash or pruritus, and none of the reports described systemic or anaphylactic reactions. A total of 35 skin tears were reported; the skin tears all occurred during the finger extension procedure. Most skin tears healed without intervention, although two patients received a skin graft. The treating physician for one patient noted that although the tear was granulating and beginning to heal, the patient (also a physician) did not want to wait and insisted on a skin graft. The second skin graft case involved an 80-year-old man who experienced a skin tear during extension. The treating physician reported that the large wound required skin grafting and the procedure was successful. There were two reports of hypoesthesia involving the injected hand that resolved; however, there were no reports of nerve injury. In one case, the reporting physician stated his belief that the hypoesthesia was related to a tight splint.

Here, we describe the two flexor tendon ruptures and one flexor pulley injury reports:

Case 1. A flexor tendon rupture occurred in a 61-year old man who received CCH for the treatment of a cord involving the PIP joint of the fifth finger of the left hand. At a 2-week follow-up appointment after collagenase injection, the patient's fifth finger was straight but would not bend actively. Profundus tendon rupture was confirmed with ultrasound and tendon graft procedure was scheduled for 1 month after diagnosis of the tendon rupture. No additional follow-up information was reported.

Case 2. A flexor tendon rupture occurred in a 71-year-old man who received CCH to treat a 30° MP cord involving the left ring finger. Approximately 3 months following the collagenase injection, rupture of the flexor digitorum superficialis tendon was diagnosed via physical exam. It was stated that no corrective procedures were planned or undertaken at the time of the report.

Case 3. A flexor pulley injury was reported in a 52-year-old woman who received CCH injection to treat a cord affecting the MP joint of the right ring finger. Following the finger extension procedure, the patient was unable to completely flex her MP joint—there was a 50% decreased range of motion. A magnetic resonance imaging (MRI) scan was ordered, which showed increased distance between the bone and flexor tendons consistent with A2 pulley incompetence. Clinically, the patient improved, but she could not completely flex the MP joint. No further follow-up information was reported.

Discussion

Post-marketing safety data received by the manufacturer for CCH in the first year following product approval and launch in the USA showed a safety profile similar to that

demonstrated in CCH clinical trials [10, 11]. Local, non-serious effects from treatment were the most frequent reports received. No systemic allergic hypersensitivity or anaphylactic reactions were reported. Notable but rare AEs included two flexor tendon ruptures and one A2 flexor pulley injury. Although skin tears occurring during the finger extension procedure have been reported from clinical trials, two were reported to have been treated with skin grafting in post-marketing use.

Flexor tendon and A2 pulley rupture associated with CCH treatment are uncommon, representing a reporting rate of 0.6 per 1,000 injections. In the current analysis, the tendon rupture reporting rate was 0.37 per 1,000 injections. The post-approval use included physicians who—although experienced hand surgeons trained in the CCH treatment procedure—had not previously used CCH (unlike the clinical investigators in the two clinical trials). Of note, one comprehensive review of major surgical and post-operative complications found an average of 15.7% (range 3.6–39.1%) of patients undergoing fasciectomy (37 studies) or aponeurotomy (4 studies) experienced major complications, including, on average, wound healing complications (22.9%), incisional scar pain (17.4%), dyesthesias/paresthesias (13.5%), hypoesthesia (10.1%), “flare” reaction of aggressive fascial proliferation and nodule/cord formation (9.9%), complex regional pain syndrome (5.5%), defined iatrogenic digital nerve injury (3.4%), digital artery injury (2%), infection (2.4%), and hematoma (2.1%) [6]. Similar to functional reconstruction of digital nerve and artery injuries following fasciectomy, tendon ruptures and flexor pulley injury following CCH treatment can potentially be functionally reconstructed [14].

The information presented in this report must be interpreted in the proper context because it is based upon spontaneously reported post-marketing data, which only allow for calculation of reporting rates, as opposed to incidence rates. One limitation of the current evaluation is that all of the adverse event and follow-up recovery or treatment information may not have been reported and available for analysis. For example, in case 3, the biomechanical relationship between MRI-diagnosed A2 pulley incompetence and partial loss of MP flexion is not clear. Moreover, the nature of the US spontaneous reporting system does not allow for calculation of true incidence and confirmation of diagnosis. However, reports received from post-marketing monitoring are valuable in that they play a critical role in the 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 [1]. While acknowledging the limitation that physicians or patients must report AEs, post-marketing monitoring may actually be better suited to capture rare AEs that may not be detected in clinical trials with their relatively small numbers of patients and short duration follow-up.

In conclusion, the AEs reported during the first post-marketing year for CCH were similar in type and severity to those reported in clinical trials. Local, nonserious reactions to treatment were most commonly reported, and no safety-related changes needed to be made to the product label. Serious AEs associated with CCH were reported infrequently and are less common than the documented major complications reported from surgical treatments.

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Conflict of interest C. A. P. is a consultant for Auxilium Pharmaceuticals, from which he has received honoraria and reimbursement for travel and accommodation expenses. G. J. F.'s employer, SSI Strategy, has received consulting fees or honoraria and travel and expenses reimbursement from Auxilium Pharmaceuticals, where he served as a safety consultant. C. A. M. is an employee of Auxilium Pharmaceuticals, where she is the Director of Drug Safety.

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