Introduction

Dupuytren’s contracture (DC) involves pathologic myofibroblast forming cords due to deposition of collagen into the digitopalmar fascia (Badalamente et al., 1983; Hurst et al., 1986), which can result in fixed flexion deformity of the affected finger impairing normal hand function (Rayan, 2007; Shaw et al., 2007; Thurston, 2003). The traditional treatment option for DC has involved surgical removal or disruption of fascial cord to allow release of the contracture (Crean et al., 2011; Dias and Braybrooke, 2006). An alternative nonsurgical treatment for DC is collagenase Clostridium histolyticum (CCH), which is injected directly into the cord to weaken it by enzymatic degradation, allowing the treating physician to manipulate and break the cord (Gilpin et al., 2010; Hurst et al., 2009).

No clinical trials have compared side effects of these two treatment methods. One systematic review of treatment outcomes for DC found that different types of complications occurred in partial surgical fasciectomy compared with CCH treatment (Chen et al., 2011). Fasciectomy complications included nerve laceration, neurapraxia, infection and chronic regional pain syndrome, whereas CCH treatment complications mostly comprised skin tears, although these were the only five types of complications that this study reported. However, due to their inclusion criteria, Chen et al. only included six open safety and tolerability of collagenase Clostridium histolyticum and fasciectomy for Dupuytren’s contracture

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Abstract

Safety was evaluated for collagenase Clostridium histolyticum (CCH) based on 11 clinical trials (N = 1082) and compared with fasciectomy data in a structured literature review of 48 European studies (N = 7727) for treatment of Dupuytren’s contracture. Incidence of adverse events was numerically lower with CCH vs. equivalent complications from fasciectomy [median [range] incidence], including nerve injury [0% vs. 3.8% [0%–50%]], neurapraxia [4.4% vs. 9.4% [0%–51.3%]], complex regional pain syndrome [0.1% vs. 4.5% [1.3%–18.5%]] and arterial injury [0% vs. 5.5% [0.8%–16.5%]]. Tendon injury [0.3% vs. 0.1% [0%–0.2%]], skin injury [16.2% vs. 2.8% [0%–25.9%]] and haematoma [77.7% vs. 2.0% [0%–25%]] occurred at a numerically higher incidence with CCH than surgery. Adverse events in CCH trials not reported after fasciectomy included peripheral oedema; extremity pain; injection site pain, haemorrhage and swelling; tenderness; pruritus and lymphadenopathy. CCH-related adverse events were reported as predominantly injection-related and transient. These results may support clinical decision-making for treatment of Dupuytren’s contracture.

Keywords
Collagenase Clostridium histolyticum, Dupuytren’s contracture, fasciectomy, safety

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fasciectomy studies (range 37–261 patients) and four CCH trials (range 13–204 patients).

Crean et al. (2011) evaluated safety outcomes following fasciectomy in patients with DC, using a systematic search and identification approach of 48 fasciectomy studies, which was used in this analysis as the source of fasciectomy surgical complication data. The objective of the current analysis was to evaluate detailed information on short-term safety following fasciectomy in the structured review and present these detailed information on short-term safety following fasciectomy in patients with DC, using a systematic search and identification approach of 48 fasciectomy studies, which was used in this analysis as the source of fasciectomy surgical complication data.

Methods

Clinical trial data on collagenase Clostridium histolyticum

Safety data, including adverse events (AEs), were evaluated from all patients who entered the clinical trials and received at least one injection of CCH. This population comprised patients from 11 clinical studies (ClinicalTrials.gov identifier), including one Phase I (NCT00528931), one Phase II (NCT00004409), and nine Phase III trials (NCT00528840, NCT00528606, NCT00528424, NCT00533273, NCT00260429; four trials did not have ClinicalTrials.gov identifiers). Table 1 provides a general overview of each of the studies in these analyses, including designs, CCH doses, patient numbers, sex distribution, ages and eligibility criteria.

Surgical fasciectomy data

The source of data on fasciectomy for this article was the structured review, which identified and evaluated 48 studies (in English, French, German, Italian, Spanish, Swedish and Dutch, published since 1980) with data on safety outcomes following limited, total or unspecified fasciectomy or dermo-fasciectomy treatment of DC, using systematic search and identification criteria (Crean et al., 2011). For this analysis, fasciotomy and needle aponeurotomy were not included.

These surgical complications reported from published fasciectomy studies were evaluated and compared with those with treatment-related AEs from the CCH clinical trials. As nonclinical trial publications, the fasciectomy reports did not adhere to Medical Dictionary for Regulatory Activities (MedDRA) coding, so MedDRA Preferred Terms from the CCH clinical trials were compared with the closest equivalent complications reported in the fasciectomy studies.

Statistical analyses

No statistical analysis was possible, as the data from the individual fasciectomy studies were not available. Because of the heterogeneity of the source data, only descriptive statistics (e.g. incidences, median and ranges) are reported for published literature on surgical fasciectomy and CCH clinical trial data.

Results

The CCH safety population comprised 1082 patients with DC. The fasciectomy studies included 7727 patients who had data on complications associated with surgical fasciectomy.

The incidence of AEs in CCH-treated patients and equivalent fasciectomy complications are presented (Table 2). These CCH-related AEs generally occurred at a lower incidence than equivalent fasciectomy complications. CCH-treated patients experienced smaller incidences (%) of the following AEs vs. patients treated with fasciectomy (median % [range]): nerve injury (0% vs. 3.8% [0–50%]), neurapraxia (4.4% vs. 9.4% [0–51.3]), complex regional pain syndrome (0.1% vs. 4.5% [1.3–18.5]) and arterial injury (0% vs. 5.5% [0.8–16.5%]). Incidence of tendon injury (0.3% vs. 0.1% [0–0.2]), skin injury (16.2% vs. 2.8% [0–25.9]) and haematoma (77.7% vs. 2.0% [0–25]) were numerically higher with CCH treatment vs. surgery, with the most frequent skin-related and haematoma-related AEs in CCH-treated patients being skin lacerations (11.1%) and contusions (54.5%), respectively.

The ‘other’ category shows the remainder of the CCH-related AEs that occurred at a frequency ≥2%, but did not have equivalent fasciectomy complications reported in the structured review (Table 2). The most common (occurring in >10% of CCH-treated patients) of these ‘other’ AEs included oedema peripheral, injection site pain, pain in extremity, injection site haemorrhage, tenderness, injection site swelling, pruritus and lymphadenopathy. All of these ‘other’ treatment-related AEs were deemed by the clinical trial investigators to be possibly or probably related to the actual injection procedure. The majority of these CCH-related AEs were considered to be mild or moderate in intensity and were transient, with most such AEs resolving within 7–10 days.

Discussion

Most AEs associated with CCH occurred at a lower incidence than complications reported for fasciectomy (e.g. CCH [%] vs. fasciectomy [median %]): arterial injury 0% vs. 5.5%; nerve injury 0% vs. 3.8%). These AEs were generally reported in the clinical trials as due to the actual CCH injection procedure, as well as the pharmacodynamic properties of CCH, which have demonstrated inability to digest type IV collagen in these structures (Miyoshi et al., 1998). Whereas one could hypothesize that an injection in a metacarpophalangeal (MP) joint contracting cord would be
| Study ID       | Phase | Study design                                                                 | CCH dosing                                      | Patients entered/completed, n | Sex: M/F, n | Mean age, y [range] | Key eligibility criteria                                                                                                                                 |
|---------------|-------|-------------------------------------------------------------------------------|-------------------------------------------------|------------------------------|-------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| AUX-CC-855    | 1     | Single centre (US), 12 months, open label, PK and safety                       | 0.58 mg (10,000 U) injection                    | 16/15                        | 15/1        | 60.6 (36–90)      | Aged ≥18 y, with DC, with a primary MP or PIP joint contracture suitable for injection and evaluation                                                |
| DUPY-202      | 2     | Multicentre [2 US sites], 12 months, double-blind, randomized, placebo-controlled, dose response, followed by an open-label phase | One injection in 0.25 ml (MP) or 0.20 ml (PIP) of 2500, 5000 or 10,000 U | 2500 U: 18/13 2500 U: 15/3   | 2500 U: 64.5 (50–82) 2500 U: 63.5 (44–78) | Aged ≥18 y with DC with a fixed flexion deformity of the fingers ≥20–30° caused by a palpable cord                                                   |
| DUPY-303      | 3     | Single centre [US], 3 months [with up to 5-y follow-up], double-blind, randomized, placebo-controlled | One 10,000 U injection in 0.25 ml (MP) or 0.20 ml (PIP) | 23/21                        | 20/3        | 60.1 (45–73)      | Aged ≥18 y with DC with a fixed flexion deformity of the fingers ≥20° caused by a palpable cord                                                                 |
| DUPY-404      | 3     | Single centre [US], open-label extension study [up to 5-y follow up]          | One 10,000 U injection in 0.25 ml (MP) or 0.20 ml (PIP) | 19/18                        | 14/5        | 63.9 (45–82)      | Aged ≥18 y with DC with a fixed flexion deformity of the fingers ≥20° caused by a palpable cord. Patients must have participated in DUPY-303, completed the 30-day post last treatment follow-up visit provided 90 days post first treatment had elapsed and must have received the last injection within the last 3 months. |
| AUX-CC-851/ 852| 3     | Multicentre [3 US sites], 12 months, double-blind, randomized, placebo-controlled, open label | 0.58 mg (10,000 U) injection: 0.25 ml (MP) or 0.20 ml (PIP) | 5/1                          | 4/1         | 59.8 (46–66)      | Aged ≥18 y with DC with a fixed flexion deformity of the finger(s) ≥20° or ≤100° for MP (≤80° for PIP) contracture, caused by a palpable cord |
| AUX-CC-853    | 3     | Multicentre [2 Australian sites], 12 months, double-blind, randomized, placebo-controlled, followed by an open-label extension | 0.58 mg (10,000 U) injection: 0.25 ml (MP) or 0.20 ml (PIP) | 17/15                        | 15/2        | 62.7 (53–73)      | Aged ≥18 y with DC of an MP joint with a fixed flexion deformity of the finger(s) ≥20° or ≤100° contracture, caused by a palpable cord |

(Continued)
| Study ID   | Phase | Study design                        | CCH dosing | Patients entered/completed, n | Sex: M/F, n | Mean age, y [range] | Key eligibility criteria                                                                                                                                 |
|------------|-------|-------------------------------------|------------|------------------------------|-------------|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| AUX-CC-854 | 3     | Multicentre (20 Australian and European sites), 9 months, open label | 0.58 mg (10,000 U) injection: 0.25 ml (MP) or 0.20 ml (PIP) | 386/358       | 334/52         | 63.2 (35–86)    | Aged ≥18 y with DC, with a fixed flexion (i.e. ≥20 but ≤80 for PIP joint; ≥20 but ≤100 for MP joint) deformity of ≥1 finger, other than the thumb, caused by a palpable cord. Patients were CCH treatment-naïve or had received ≤2 injections of CCH. |
| AUX-CC-856 | 3     | Multicentre (14 US sites), 9 months, open label | 0.58 mg (10,000 U) injection: 0.25 ml (MP) or 0.20 ml (PIP) | 201/168       | 164/37         | 64.7 (39–87)    | Aged ≥18 y, with DC, with a fixed-flexion (i.e. ≥20 but ≤80 for PIP joint; ≥20 but ≤100 for MP joint) deformity of ≥1 finger, other than the thumb, caused by a palpable cord. Patients were CCH treatment-naïve or had received ≤2 injections of CCH. |
| AUX-CC-857 | 3     | Multicentre (16 US sites), 3 months, randomized, double-blind, placebo-controlled | 0.58 mg (10,000 U) injection: 0.25 ml (MP) or 0.20 ml (PIP) | 204/191       | 171/33         | 62.3 (33–89)    | Aged ≥18 y, with DC, with a primary MP or PIP joint contracture suitable for injection and evaluation                                                                 |
| AUX-CC-858 | 3     | Multicentre (16 US sites), 9 months, open label, extension | 0.58 mg (10,000 U) injection: 0.25 ml (MP) or 0.20 ml (PIP) | 286/245       | 245/63         | 62.7 (33–89)    | All patients who completed the 90-day visit after their initial injection in study AUX-CC-857                                                                 |
| AUX-CC-859 | 3     | Multicentre (5 Australian sites), 12 months, randomized, double-blind, placebo-controlled, followed by an open-label extension phase | 0.58 mg (10,000 U) injection: 0.25 ml (MP) or 0.20 ml (PIP) | 45/45         | 39/6           | 63.0 (45–88)    | Aged ≥18 y, with DC, with a primary MP or PIP joint contracture suitable for injection and evaluation                                                                 |

CCH: collagenase Clostridium histolyticum; DC: Dupuytren’s contracture; MP: metacarpophalangeal joints; PIP: proximal interphalangeal; PK: pharmacokinetic.
Table 2. AEs or complications occurring with fasciectomy from the European structured review and in the CCH clinical trials.

| Fasciectomy surgery AE or complication | CCH treatment (N = 1082) |
|----------------------------------------|--------------------------|
| Surgery type                           |                          |
| All surgery types, median [%]          | Individual study estimates (%) AE* |
| Complex regional pain syndrome         |                          |
| Limited                                | 4.5                      |
| Dermofasciectomy                       | 2.6                      |
| Not specified                          | 2.3                      |
| Pain                                   | 20.4                     |
| Total                                  | 82.517 and 8517          |
| Arterial injury                        |                          |
| Limited                                | 5.5                      |
| Not specified                          | 16.519 and 1219; 9.028 and 2.020 |
| Haematoma                              | 2.0                      |
| Dermofasciectomy                       | 14.924                   |
| Total                                  | 7.725; 1.917 and 017     |
| Neurapraxia                            | 9.4                      |
| Dermofasciectomy                       | 51.310; 38.510; 2.511; 024 |
| Total                                  | 9.425 and 1.525          |
| Not specified                          | 4627 and 2627; 45.719    |
| Nerve injury                           | 3.8                      |
| Dermofasciectomy                       | >5014 and 41.154         |
| Total                                  | 12.525; 9.425; 6.225; 4.625; 3.525 and 1.525; 9.624 and 4.224 |
| Skin injury                            | 2.8                      |
| Dermofasciectomy                       | 25.9; 6.9; 5.018; 4.21 and 321; 2.815; 2.613; 2.411 and 1.211; 1.031.10; 0.96; 0.4; 0.3; 01.6; 06 |
| Total                                  | 12.517 and 7.717; 1.525 |
| Not specified                          | 1414                     |

(Continued)
less likely to result in nerve injury compared with a proximal interphalangeal (PIP) joint contracting cord, among 1082 patients in the pooled CCH studies, no nerve injuries were reported even when PIP injections were administered. For example, the number of CCH injections in four CCH phase 3 clinical trials totalled 684 (MP cords) and 443 (PIP cords) (Gilpin et al., 2010; Hurst et al., 2009; Witthaut et al., 2013).

When comparing CCH incidence with fasciectomy (median incidence), the rates of tendon injury [0.3%...
contracture angle of 79.3% at 30 days after the last treatment has been shown to result in a change of effectiveness with CCH trials (Gilpin et al., 2010; Hurst et al., 2009; Witthaut et al., 2011). For example, in all primary joints, CCH fasciectomy reported in the structured review (Crean et al., 2013) appeared similar to effectiveness with fasciectomy in incidence of tendon injury has meaningful clinical or statistical significance. In our clinical experience, observed skin lacerations likely relate to post-anaesthesia manipulations to break the cord by passive finger extension. Use of local anaesthesia prevents potential pain or discomfort related to the finger extension procedure. The various degrees of adherence of the Dupuytren’s cord to the overlying skin may leave certain areas of skin frail because of the underlying condition. Therefore, manipulations may lead to skin tears in the anesthetized area. These lacerations typically heal in a short time without any additional medical intervention. All surgeries, of course, require intentional skin incision, so ‘skin injury’ and/or haematoma would be the rule, not the exceptional complication.

In other published studies of patients with primary and recurrent DC who underwent fasciectomy, scar hypertrophy (one study, 1/10 [10%] patients), scar contracture (one study, 3/32 [9%]), incisional scar pain (one study, 4/23 [17%]), joint stiffness (two studies, 55/356 [15%]) and cold intolerance (one study, 3/15 [20%]) have been reported (Denkler, 2010). None of the complications, however, occurred at a clinically significant incidence in the CCH clinical trials. Although the variability in incidence for some of the CCH AEs and equivalent fasciectomy complications appeared to be small, these differences could still be factored into the process of clinical decision-making when choosing a therapy that suits the needs of an individual patient with DC. Overall, CCH appeared to have a generally better safety profile than fasciectomy; this may have important clinical relevance because published efficacy outcomes in CCH clinical trials (Gilpin et al., 2010; Hurst et al., 2009; Witthaut et al., 2013) appeared similar to effectiveness with fasciectomy reported in the structured review (Crean et al., 2011). For example, in all primary joints, CCH treatment has been shown to result in a change of contracture angle of 79.3% at 30 days after the last injection (Hurst et al., 2009; Witthaut et al., 2011), whereas the reported mean improvement with fasciectomy was 76% (Crean et al., 2011). In addition, the average recurrence rate across fasciectomy studies was ~39% at a median time of 4 years; however, only 14% of these studies included time-to-event data in their recurrence rates. In a recent study, 65% of CCH-treated DC joints exhibited a durable correction for 3 years after treatment, with only 7% requiring surgical or medical intervention during the 3-year follow-up period (Peimer et al., 2012a; Peimer et al., 2012b).

The CCH safety profile has been further evaluated in the US real-world clinical setting. During the first year after regulatory approval of CCH, the most commonly reported US post-marketing treatment-emergent AEs (incidence rate per 1000 doses) were skin lacerations (6.5); oedema peripheral (5.6); confusion (4.8); injection site haematoma (1.9); lymphadenopathy (1.5); pain in extremity (1.5); blood blister (1.5); injection site pain (1.3); and tenderness (1.1) (Peimer et al., 2012b). Other notable real-world AEs included two cases of tendon ruptures and one flexor pulley injury (0.6 per 1000 injections). However, under-reporting of complications in a real-world treatment setting cannot be fully ruled out as a potential confounding factor in both CCH and surgical cases (e.g. by a patient not wishing to complain; by a surgeon not willing to share less-than-successes or who simply considers the complication to be an expected effect of the particular intervention). In addition, the phase IIIb POINT X (Prospective, Open-label Investigation of the Nonsurgical Treatment with collagenase Clostridium histolyticum (Xiapex®)) study evaluated 254 patients across 28 real-world European settings and found that CCH was generally well tolerated (Warwick et al., 2014). Most AEs in POINT X were consistent with the CCH phase III studies and typically comprised transient injection site reactions.

These analyses have limitations, as the fasciectomy data were derived from the published literature, all comparisons are qualitative and no direct inferential statistical analyses could be performed. Data on individual patients in these published studies were not available, limiting the ability to pool the fasciectomy data optimally. For example, in order to calculate a reliable estimate of number needed to harm for the fasciectomy complication rates, it would have been necessary to compute a credible point estimate for each complication that summarized the overall experience across all studies. Due to the heterogeneity of the source studies, that was not possible. In addition, the fasciectomy structured review included patients who underwent dermofasciectomy as well as limited fasciectomy; based on our clinical experience, we believe the complication rate between these two
procedures would likely differ and could affect the results. Moreover, follow-up times in the fasciectomy publications varied by the individual cases included, or by the study designs, which makes interpretation of the complication rates difficult across these studies. In addition, since this was not a head-to-head clinical trial, variability between the subjects should be expected due to a lack of consistent predefined inclusion and exclusion criteria across studies. Next, the fasciectomy structured review included both interventional and observational studies, which did not always specifically code AEs using pre-defined classifications that are used in clinical trials [e.g. MedDRA]. Moreover, the fasciectomy review did not distinguish between types of AEs [e.g. AEs vs. serious AEs] or their severity, which makes detailed comparisons difficult. However, we have made every effort to compare specific MedDRA-coded AEs from the CCH clinical trials with equivalent surgical complications associated with fasciectomy in a clinically relevant manner.

Although these findings are subject to the above limitations, the numerically lower incidence of most AEs with CCH therapy [vs. fasciectomy] may become a useful factor in clinical decisions made by healthcare providers considering which treatment to choose for a patient’s DC. We believe that these results have relevance for discussing with patients each treatment’s risk–benefit characteristics and in considering the differences in the safety profiles to help decide which treatment option is the most suitable for each particular patient.

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Conflict of interests
- Dr Peimer has received honoraria and travel reimbursements from Pfizer and Auxilium.
- Dr Wilbrand is a study investigator for Auxilium Pharmaceuticals and has received honoraria and travel reimbursements from Pfizer and Auxilium for consultancies.
- Drs Gerber and Szczyapa and Mr Chapman are full-time employees of Pfizer.

Ethical approval
All collagenase Clostridium histolyticum clinical trials included in this manuscript were approved by an institutional review board for each of the participating centers and adhered to ethical principles described by Good Clinical Practices, the International Conference on Harmonisation Guidelines, and the Code of Federal Regulations title 21. All patients provided written informed consent to participate in the trials. Ethics approvals were not required for the fasciectomy studies, as they were reviewed from already published clinical reports without additional issues of patient consent or confidentiality.

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