Collagenase Clostridium Histolyticum for the Treatment of Dupuytren's Disease: A Delphi Report

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INTRODUCTION

- Dupuytren's disease (DD) is a heterogenous fibroproliferative condition of the palmar fascia that is characterized by the development of fascial nodules and cords that result in digital contracture affecting hand function[1,2]
- Although treatment guidelines for DD are currently lacking, reflecting the variable disease course experienced by patients, multiple treatment options are available to surgeons, including[1,3]:
  - Observation
  - Nonsurgical interventions (eg, radiotherapy, steroid injections, splinting, collagenase clostridium histolyticum injection [CCH; Xiaflex®; Endo Pharmaceuticals Inc., Malvern, PA])
  - Surgical interventions (eg, percutaneous aponeurotomy, fasciectomy, dermofasciectomy, dynamic external fixation, digital amputation)
- Although the efficacy of injectable CCH was demonstrated in two phase 3 studies,[3,4] the appropriate role of injectable CCH for the treatment of DD is unclear, given the absence of evidence-based differential treatment guidelines
  - Two phase 3 studies demonstrated the efficacy of injectable CCH for decreasing contractures and improving range of motion in patients with DD[4,5]
  - Post hoc analysis of a phase 3 study[4] demonstrated the efficacy of injectable CCH for improving contracture in patients with varying severities of DD[6]

AIM

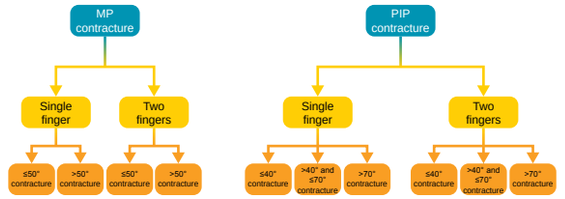
- To develop consensus recommendations among an expert panel of hand surgeons on the appropriate treatment of DD with CCH in well-defined patient populations with varying degrees of disease severity and functional impairment

METHODS

- A modified Delphi method employing 3 successive online survey rounds was used to capture the clinical expertise of panelists and to determine if consensus could be reached regarding use of CCH for the treatment of DD
- Round 1 utilized 22 real-world case scenarios to determine the panelists' recommendations for using CCH to treat metacarpophalangeal (MP) and/or proximal interphalangeal (PIP) joint contractures involving a single finger or 2 fingers, with varying degrees of contracture and clinical severity (Figure 1A)
  - Each scenario presented a distinct contracture(s) with a series of statements to evaluate the impact of patient- or disease-related features (ie, age, recurrence, risk of anesthesia, diathesis, poor-quality skin, post-fasciectomy scarring) on the clinical decision to use CCH (Figure 1B)
  - Appropriate use of CCH for the treatment of thumb contractures and in patients who are on blood thinners other than aspirin also was explored

Figure 1. Overview of Clinical Scenarios

A. Scenarios examined for MP and PIP contractures alone and in combination



B. Patient- and disease-specific factors

Factors	
Treatment with CCH for the specific scenario	Recurrence with poor-quality skin and/or significant post-fasciectomy scarring
Age ≥65 years	
Boutonnière deformity (only for PIP scenarios)	Recurrent contracture previously treated with CCH
Thick pretendinous cord	Significant medical risk for anesthesia
Recurrence without post-fasciectomy scar tissue	Severe diathesis

CCH = collagenase clostridium histolyticum; MP = metacarpophalangeal; PIP = proximal interphalangeal.

- Responses were captured using a 5-point Likert scale ("strongly agree," "agree," "deficient information," "disagree," and "strongly disagree")
- Level of agreement for each statement was determined, with a consensus threshold of ≥66.7% for agreement ("strongly agree" and "agree") or disagreement ("strongly disagree" and "disagree")

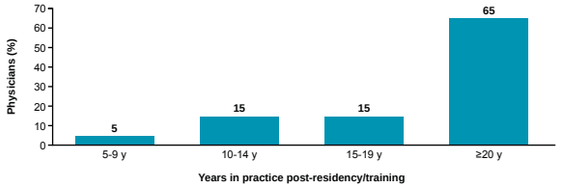
RESULTS

Panelist Characteristics

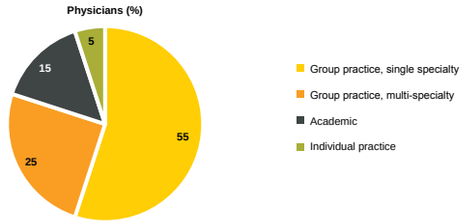
- Of the 33 hand surgeons who were invited based on their expertise in DD, 22 agreed to participate in the survey, 20 of these completed Round 1 of the survey, and 19 of these completed Round 2
  - Overall, 80% had practiced medicine for ≥15 years and all had completed a fellowship in hand surgery (Figure 2)
  - 90% were certification of added qualification-certified hand surgeons

Figure 2. Panelist Characteristics

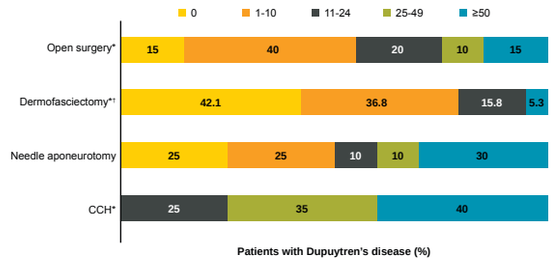
A. Professional experience



B. Practice setting



C. Utilization of specific treatments for patients with Dupuytren's disease

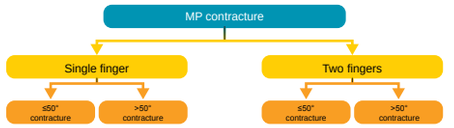


*Restricted to the past year.
†n=19.
CCH = collagenase clostridium histolyticum.

Clinical Scenarios (Round 1)

- Among the 22 clinical scenarios evaluating patients with palpable cord(s) who present with MP or PIP joint contractures, 85.8% of statements achieved consensus for agreement
  - These results include the finding that 80% of respondents defined a thick cord as >4 mm or >5 mm
  - There was no consensus for disagreement for any of the statements
- Panelists achieved consensus that CCH was an appropriate therapeutic intervention for patients with a palpable cord with single-finger or 2-finger MP joint contractures (Figure 3)

Figure 3. Consensus for Use of CCH With Clinical Scenarios Regarding Patients With MP Joint Contracture



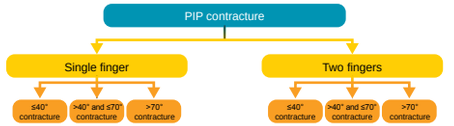
Single finger with MP joint contracture ≤50° or >50°
OR
2 fingers, each with MP joint contracture ≤50°

- 1 or 2 MP contractures ≤50° or >50°
- 1 or 2 MP contractures ≤50° or >50° that has single, thick pretendinous cord
- 1 or 2 recurrent MP contractures ≤50° or >50° without post-fasciectomy scar tissue
- 1 or 2 recurrent MP contractures ≤50° or >50° with poor-quality skin and/or significant post-fasciectomy scarring
- 1 or 2 recurrent MP contractures ≤50° or >50° previously treated with CCH
- 1 or 2 recurrent MP contractures ≤50° or >50° and significant medical risk for anesthesia
- 1 or 2 MP contractures ≤50° or >50° with severe diathesis

CCH = collagenase clostridium histolyticum; MP = metacarpophalangeal.

- Consensus for use of CCH was reached for most statements among the PIP joint contracture scenarios (Figure 4)
  - For the clinical scenario related to patients with 2 fingers, each with a PIP joint contracture >70° and no boutonnière deformity, panelists achieved consensus for:
    - Two PIP contractures >70°
    - Two PIP contractures >70° that have thick cords
    - Two recurrent PIP contractures >70° without post-fasciectomy scar tissue
    - Two PIP contractures >70° and significant medical risk for anesthesia

Figure 4. Consensus for Use of CCH With Clinical Scenarios Regarding Patients With PIP Joint Contracture



Single finger with a PIP joint contracture ≤40°
Single finger with a PIP joint contracture >40° and ≤70° and no boutonnière deformity
Single finger with a PIP joint contracture >70° and no boutonnière deformity
2 fingers, each with a PIP joint contracture ≤40° and no boutonnière deformity
2 fingers, each with a PIP joint contracture >40° and ≤70° and no boutonnière deformity

- One or 2 PIP contractures ≤40° or one PIP contracture >40° and ≤70° or >70°
- One PIP contracture ≤40°, >40° and ≤70°, or >70° that has a single, thick cord
- Two PIP contractures ≤40° that have thick cords
- One or 2 recurrent PIP contractures ≤40° or one recurrent PIP contracture >40° and ≤70° or >70° without post-fasciectomy scar tissue
- One or 2 recurrent PIP contractures ≤40° or one recurrent PIP contracture >40° and ≤70° or >70°previously treated with CCH
- One or 2 recurrent PIP contractures ≤40° or one recurrent PIP contracture >40° and ≤70° or >70° and significant medical risk for anesthesia
- One or 2 PIP contractures ≤40° or one PIP contracture >40° and ≤70° or >70° and severe diathesis

CCH = collagenase clostridium histolyticum; PIP = proximal interphalangeal.

- Of the 18 scenarios describing PIP contractures either alone or in combination with MP contractures, 17.3% of statements did not achieve consensus
- All scenarios for patients with an MP and/or interphalangeal thumb contracture reached consensus for agreement for use of CCH
- Panelists agreed that their clinical judgment for the use of CCH would not change for patients ≥65 years of age or based on cord thickness
- Clinical scenarios describing PIP contractures associated with "poor-quality skin," "scarring," and "boutonnière deformity" that failed to achieve consensus during Round 1 were revised for Round 2 to include additional context for clarity
  - 77.3% of scenarios that contained statements related to "poor-quality skin" and "scarring" did not achieve consensus
  - Consensus was not achieved in some scenarios if the patient had a boutonnière deformity (eg, one finger with an MP contracture >50° and a PIP contracture >40° and ≤70° [60% agreement]; one finger with an MP contracture >50° and the other with a PIP contracture >70° [60% agreement])

Clinical Scenarios (Round 2)

- In addition to clinical scenarios describing PIP contractures that were revised based on lack of consensus in Round 1, the "impact of patient decision" (ie, the patient does not want an open surgical procedure) in the PIP scenarios was assessed
  - Nearly all scenarios achieved 100% consensus for use of CCH (Table 1)

Table 1. Modified Clinical Scenarios and Consensus Achieved

Category	Clinical scenario	Statements reaching consensus for agreement (%)
Poor-quality skin	Based on your clinical experience and current practice, CCH is an appropriate therapeutic intervention for patients who present with recurrent PIP contracture(s) with poor-quality skin (ie, deficient skin) and *distinct* palpable cord(s).	
	• Following the manipulation, the patient will develop *a minor skin tear with NO exposed tendon.*	100
	• Following the manipulation, the patient will develop *a major skin tear with exposed tendon.*	88.2
Post-fasciectomy scarring	Based on your clinical experience and current practice, CCH is an appropriate therapeutic intervention for patients who present with recurrent PIP contracture with significant *post-fasciectomy scarring* and distinct palpable cord(s).	100
Impact of patient decision	Based on your clinical experience and current practice, CCH is an appropriate therapeutic intervention for patients who present with the following contracture severities, and *in addition to the clinical findings, the patient does not want an open surgical procedure.*	100
Boutonnière deformity	Would your clinical judgment for the use of CCH for the following contracture severities change if the patient had a boutonnière deformity that you would treat at the same time (eg, CCH and terminal extensor tenotomy under local anesthesia at the time of manipulation)?	100

CCH = collagenase clostridium histolyticum; PIP = proximal interphalangeal.

- Both of the clinical scenarios related to "two fingers, each with a PIP joint contracture >70° and no boutonnière deformity" presented in Round 1 that were reassessed without modification achieved consensus for use of CCH
  - Two recurrent PIP contractures >70° previously treated with CCH
  - Two PIP contractures >70° and severe diathesis
- Panelists achieved consensus regarding the use of CCH in patients receiving a blood thinner other than aspirin presenting with contractures that require 1 vial of enzyme (in Round 1) and 2 vials of enzyme (in Round 2)
- At the end of Round 2, 4.7% of statements had not achieved consensus (Table 2)
  - The statements related to poor-quality skin are being assessed in Round 3

Table 2. Statements Failing to Achieve Consensus* (Round 2)

Scenario	Statement	Agreement in Round 2, n (%)†
Poor-quality skin	Based on your clinical experience and current practice, CCH is an appropriate therapeutic intervention for patients who present with recurrent PIP contracture(s) with poor-quality skin (ie, deficient skin) and *distinct* palpable cord(s)	
	• Two fingers, each with a PIP joint contracture >70° and no boutonnière deformity	12 (63.2)
	• Two fingers, one with an MP contracture ≤50° and the other with a PIP contracture >70° and no boutonnière deformity	12 (63.2)
Garrod's nodules	If you have injected what you think is necessary and have some left-over CCH in the vial after a procedure, would you use it to treat Garrod's nodules of dorsal PIP joints? Yes	11 (57.9)
Closed capsulotomy	A patient initially presents with a contracture of 70° and, following CCH injection and manipulation, is left with a 20°contracture that you think is caused by a PIP joint volar capsular contracture. Do you always attempt a closed capsulotomy if a patient is left with a 20°contracture after PIP joint manipulation? Yes	8 (42.1)

*Consensus was defined as ≥66.7% agreement ("strongly agree" and "agree") or disagreement ("strongly disagree" and "disagree") among respondents.
†Percent of panelists.
CCH = collagenase clostridium histolyticum; MP = metacarpophalangeal; PIP = proximal interphalangeal.

SUMMARY

- Consensus data from Rounds 1 & 2 indicated a high level of consensus for using CCH for the treatment of MP joint contractures of varying severity and in patients with MP and/or interphalangeal thumb contractures
- Additional contextual data in Round 2 helped achieve consensus for using CCH for treating PIP joint contractures of varying severities
  - Statements not achieving consensus are being explored in Round 3
- Consensus-based findings among expert hand surgeons point to wide-ranging application of CCH for the treatment of DD for patients with varying degrees of disease severity and functional impairment

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DISCLOSURES

GMP reports serving on the speakers' bureau for Endo Pharmaceuticals Inc. and receiving royalties from Zimmer-Biomet for the trigger release knife. DH is an employee of Endo Pharmaceuticals Inc. JRV reports serving on the speakers' bureau for Endo Pharmaceuticals Inc. PB reports serving on the speakers' bureau for Axogen and Endo Pharmaceuticals Inc.; and owning stock in Cytori.

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