Journal of Hand Surgery Global Online xxx (2022) 1–6

Contents lists available at ScienceDirect

Journal of Hand Surgery Global Online

journal homepage: www.JHSGO.org

Original Research

Incidence of Tendon Rupture After Collagenase Clostridium Histolyticum Injection for Treatment of Dupuytren Contracture in Adults: A Postmarketing Safety Analysis

Clayton A. Peimer, MD, [*] David Hurley, MD, [†] Tina Latch, BSN, [†] Susan Scott, MSN, [†] Gary M. Pess, MD [‡]

[*] Department of Orthopaedic Surgery, Warren Alpert Medical School, Brown University, Providence, RI
[†] Department of Medical Affairs, Endo Pharmaceuticals Inc, Malvern, PA
[‡] Central Jersey Hand Surgery, Eatontown, NJ

ARTICLE INFO

Article history:
Received for publication March 14, 2022
Accepted in revised form August 29, 2022
Available online xxx

Key words:
Dupuytren contracture
Microbial collagenase
Risk evaluation and mitigation
Tendon injuries
Xiaflex

Purpose: Based, in part, on the clinical study reports of tendon rupture events after collagenase clostridium histolyticum (CCH) (Xiaflex, Endo Pharmaceuticals Inc) treatment for Dupuytren contracture (DC), a Risk Evaluation and Mitigation Strategy program was instituted in 2010 by Auxilium Pharmaceuticals (now Endo Pharmaceuticals Inc) to ensure that the benefits of CCH injection outweighed the risks when treating DC. Using the postmarketing surveillance data collected in this program, a retrospective analysis was conducted to evaluate the incidence of flexor tendon rupture after CCH treatment for DC in the clinical practice setting.

Methods: The Endo Pharmaceuticals Inc safety database was searched for cases of tendon rupture reported between February 2, 2010, and October 8, 2015. Total number of CCH treatments for DC and incidence of tendon rupture were estimated using CCH dosing derived from clinical trial experience (1.7 CCH vials/treatment) or clinical practice evidence (1.08 CCH vials/treatment).

Results: Over the 5.8-year surveillance period, 97,609 vials of CCH were distributed for the treatment of DC, equivalent to an estimated total of 57,416 treatments (at 1.7 CCH vials/treatment) or 90,378 treatments (at 1.08 CCH vials/treatment). Although CCH distribution increased during the surveillance period, reports of tendon rupture were infrequent (approximately 13 cases/y; total cases: flexor tendon, n = 57; ligament/pulley, n = 2), corresponding to a 0.10% (1.7 CCH vials/treatment) or 0.06% (1.08 CCH vials/treatment) mean estimated incidence of tendon rupture in patients with DC after CCH treatment.

Conclusions: This retrospective analysis showed that flexor tendon rupture occurred infrequently in patients with DC who were treated with CCH in real-world practice settings between 2010 and 2015. On the basis of these findings and other favorable safety evidence, the Risk Evaluation and Mitigation Strategy program requirement for CCH for the treatment of DC was ended by the US Food and Drug Administration in November 2016.

Type of study/level of evidence: Therapeutic IV.

Dupuytren contracture (DC) or disease is a progressive syndrome involving collagen coalescence in the palmar fascia, which can result in nodules; cords; and, ultimately, finger deformity.[1] Collagenase clostridium histolyticum (CCH) (Xiaflex, Endo Pharmaceuticals Inc) for injection is approved for the treatment of DC with a palpable cord as a nonsurgical, office-based, minimally invasive procedure.[2,3] Collagenase clostridium histolyticum is a combination of 2 purified bacterial collagenases (AUX-I and AUX-II), which work synergistically to hydrolyze types I and III collagen and disrupt the treated cord.[4] Several trials have shown

Declaration of interests: C.A.P. reports being a consultant for Endo Pharmaceuticals Inc. D.H. and T.L. are employees of Endo Pharmaceuticals Inc and stockholders of Endo International. S.S. was an employee of Endo Pharmaceuticals Inc at the time of the manuscript development. G.M.P. reports serving on the speakers' bureau for Endo Pharmaceuticals Inc and receiving royalties from Biomet.

Corresponding Author: Clayton A. Peimer, MD, Department of Orthopaedic Surgery, Warren Alpert Medical School, Brown University, 2 Dudley Street, Providence, RI 02905.

E-mail address: peimer@brown.edu (C.A. Peimer).

https://doi.org/10.1016/j.jhsg.2022.08.013

reduced contractures and improved range of motion in patients with DC treated with CCH, with the most commonly reported adverse events (AEs) being localized injection-site swelling, pain, bruising, pruritus, and transient regional lymph-node enlargement and tenderness.[5–9] In addition, skin tears can occur as a result of the finger extension procedure after CCH injection, particularly in patients with severe contractures and/or greater degrees of contracture correction.[10–13]

Flexor tendon or pulley ruptures, more serious AEs that result in the loss of movement, have been reported in multiple clinical trials in which CCH treatment was evaluated for DC. In a phase 3 trial, 2 cases of tendon rupture were associated with 444 CCH injections (0.45%), which occurred in 2 of 204 patients (0.98% incidence).[6] In another randomized, placebo-controlled trial, 1 flexor pulley rupture occurred in 45 cords treated with CCH.[5] An open-label trial of 60 patients receiving 2 concurrent injections (ie, "double-dosing") with CCH reported 1 pulley and 1 flexor tendon rupture.[14] On the basis of these findings and the need to assess serious hypersensitivity reactions, the US Food and Drug Administration determined that a Risk Evaluation and Mitigation Strategy (REMS) program was required for CCH injection for DC to ensure that the benefits of treatment outweighed the risk of serious AEs.[3] The REMS program included implementation of a communication plan that informed health care providers about the risks of flexor tendon rupture and other AEs, provided educational materials (ie, a training guide and video) on the proper preparation and administration techniques for CCH injection, and described the proper finger manipulation procedure to achieve cord disruption and regain finger extension.[3] This managed distribution program enrollment process for each health care provider and their clinic resulted in a record of CCH use. Hence, the purpose of this postmarketing surveillance study was to evaluate the rate of tendon rupture associated with CCH use in clinical practice. We hypothesized that the incidence of CCH-associated tendon ruptures in clinical practice might differ (eg, be slightly higher) from that reported in clinical trials because the latter were conducted in a controlled setting.

Materials and Methods

As a part of a standard pharmacovigilance program, the manufacturer of CCH (formerly Auxilium Pharmaceuticals, now Endo Pharmaceuticals Inc) receives postmarketing safety reports related to the use of CCH from multiple sources, including spontaneous reporting, medical literature, licensing partners, and regulatory agencies. All reports, including those obtained through the manufacturer's call center, are processed, and the verbatim report is coded with Medical Dictionary for Regulatory Activities (MedDRA) classification terms. These data are entered into the Endo Pharmaceuticals Inc safety database (Argus, Oracle). An in-depth questionnaire was sent to each health care provider/reporter to obtain additional information related to each case. Up to 2 attempts were made to follow up on each case.

To meet the requirements of the REMS assessment plan, the database was searched for reports of tendon rupture occurring between February 2, 2010 (the US Food and Drug Administration approval date of Xiaflex for DC), and October 8, 2015 (end of the program report period). Search terms included the MedDRA preferred terms "ligament rupture" and/or "tendon rupture," with cases confined to those occurring within the United States. These search terms were chosen to capture all reported cases of tendon/pulley rupture during the surveillance period. In addition, the number of vials of CCH for the treatment of DC distributed via the REMS program during the surveillance period was recorded.

As an internal postmarketing surveillance effort, this retrospective analysis was exempt from patient informed consent requirements. All Health Insurance Portability and Accountability Act guidelines were followed, with all data anonymized before being entered into the database.

Data analysis

During the surveillance period, the database was searched to extract data on age, sex, the finger and joint affected, and post-rupture outcomes. The data collected were summarized using descriptive statistics. The overall mean estimated incidence of tendon rupture was calculated based on the mean number of vials of CCH used per treatment. According to real-world evidence, in a 12-month assessment of community and academic practices in the United States, physicians used a mean of 1.08 CCH injections per cord associated with a contracture.[15] In contrast, in 2 pivotal clinical trials, a mean of 1.7 CCH injections per cord was used.[2,5,6] Therefore, the mean estimated number of CCH treatments for DC per year was calculated in 2 ways, based on the following: (1) the use of 1.08 vials

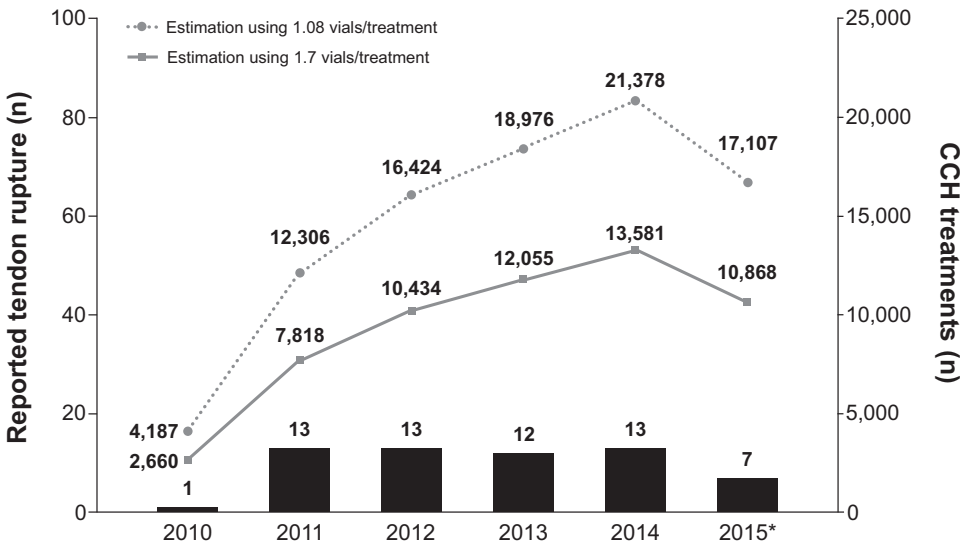

Figure 1. The number of reported tendon ruptures and the estimated number of CCH treatments for DC. The asterisk represents the year 2015 through October 8, 2015.

Table 1
Patient Demographic and Tendon Rupture Characteristics

Case No.	Age (y)	Sex	Joint	Finger	Verbatim MedDRA Term	Days From Injection to Event
1	71	Male	MCP	Ring	FDS	1
2	61	Male	PIP	Little	Tendon rupture	24
3	62	Male	MCP	Little	Tendon rupture	1
4	NS	Male	PIP	Little	Flexor digitorum rupture	10
5	54	Male	PIP	Little	Flexor tendon rupture	1
6	47	Male	PIP	Little	Tendon rupture	11
7	NS	NS	PIP	Little	Flexor tendon rupture	NS
8	61	Female	MCP	Middle	FDP	26
9	52	Female	MCP	Ring	Superficial tendon rupture	NS
10	69	Female	MCP	Ring	FDP	8
11	NS	NS	PIP	Ring	Pulley rupture	NS
12	65	Male	NS	Little	Tendon rupture	6
13	70	Male	MCP	Little	FDP	1
14	72	Female	MCP	Ring	Tendon rupture	NS
15	NS	NS	NS	NS	Tendon rupture	NS
16	NS	Male	MCP	NS	Tendon rupture	NS
17	NS	Male	NS	NS	Partial tendon tear	NS
18	67	Female	NS	Little	Flexor tendon rupture	NS
19	NS	Male	MCP	Little	Tendon rupture	7
20	64	Female	PIP	Little	Tendon rupture	8
21	NS	NS	NS	NS	Tendon rupture	NS
22	68	Male	MCP	Little	FDP	NS
23	80	Male	NS	Little	Bending tendon rupture	0
24	56	Male	PIP	Little	Tendon rupture	NS
25	64	Female	PIP	Little	Profundus tendon rupture	4
26	44	Male	MCP	Little	Tendon rupture	NS
27	69	Female	MCP	Little	FDP and FDS	NS
28	37	Female	MCP	Middle	Flexor tendon rupture	42
29	NS	Male	MCP, PIP	Index	Flexor tendon rupture	NS
30	NS	NS	NS	NS	Tendon rupture	NS
31	60	Male	NS	NS	Bicep tendon rupture	NS
32	62	Male	MCP	Ring	Distal flexor tendon rupture	NS
33	52	Male	PIP	Index	Tendon rupture	2
34	60	Male	MCP	Little	Tendon rupture	NS
35	NS	Male	PIP	Little	FDP	NS
36	76	Male	PIP	Little	FDP	9
37	57	Male	PIP	Ring	Pulley rupture	NS
38	68	Female	MCP	Little	Profundus tendon rupture	1
39	NS	Female	PIP	NS	Tendon rupture	NS
40	65	Female	MCP	Ring	Tendon rupture	8
41	NS	NS	NS	NS	Tendon rupture	NS
42	NS	Female	PIP	Ring	Tendon rupture	NS
43	NS	NS	NS	NS	Tendon rupture	NS
44	64	Male	MCP, PIP	Ring	Tendon rupture	112
45	NS	NS	NS	Ring	FDP	NS
46	NS	NS	MCP	Little	Tendon rupture	NS
47	NS	Male	NS	NS	Tendon rupture	NS
48	39	Female	PIP	Index	Tendon rupture	NS
49	NS	NS	NS	Little	Tendon rupture	NS
50	51	Male	PIP, MCP	Little	Profundus tendon rupture	106
51	64	Female	MCP	Middle	FDP	2
52	NS	Male	NS	Little	Tendon rupture	NS
53	55	Female	NS	Little	Tendon rupture	NS
54	67	Female	PIP	Little	Tendon rupture	1
55	NS	Male	NS	NS	Tendon rupture	NS
56	56	Female	MCP	Middle	Tendon rupture	NS
57	NS	NS	NS	NS	Tendon rupture	NS
58	72	Male	NS	Ring	Tendon rupture	NS
59	NS	Female	NS	NS	Tendon rupture	NS

FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; MCP, metacarpophalangeal joint; NS, not specified; PIP, proximal interphalangeal joint.

of CCH per treatment (according to the evidence from clinical practice) and (2) the use of 1.7 vials of CCH per treatment (based on clinical trial data). Similarly, the estimated yearly incidence and mean estimated overall incidence rates of tendon rupture from 2010 to 2015 were calculated using a mean estimated number of CCH treatments based on either 1.08 vials or 1.7 vials of CCH per treatment.

Results

During the 5.8-year surveillance period, 97,609 CCH vials were distributed for treating DC. Based on the calculation of 1.7 CCH vials per treatment, the 97,609 distributed vials corresponded to 57,416 treatments for DC during the surveillance period, whereas the calculation of 1.08 CCH vials per treatment corresponded to 90,378

Table 2
Incidence of Tendon Rupture After CCH Treatment for Dupuytren Contracture

Parameter	Surveillance Year						
	2010*	2011	2012	2013	2014	2015†	Overall Surveillance Period‡
Reported tendon ruptures, n	1	13	13	12	13	7	59
Estimation using 1.7 CCH vials per treatment for DC							
Estimated CCH treatments, n	2,660	7,818	10,434	12,055	13,581	10,868	57,416
Incidence, %	0.04	0.17	0.12	0.10	0.10	0.06	0.10
Estimation using 1.08 CCH vials per treatment for DC							
Estimated CCH treatments, n	4,187	12,306	16,424	18,976	21,378	17,107	90,378
Incidence, %	0.02	0.11	0.08	0.06	0.06	0.04	0.07
Estimation using 1 CCH vial per injection							
CCH injections, n	4,522	13,291	17,738	20,494	23,088	18,476	97,609
Incidence, %	0.02	0.10	0.07	0.06	0.06	0.04	0.06

*Beginning February 2.
†Ending October 8.
‡February 2, 2010, to October 8, 2015.

treatments for DC. The number of tendon rupture events was relatively stable over time (approximately 13 cases annually) despite the increased distribution of CCH over this time (Fig. 1).

Fifty-nine cases of flexor tendon (n = 57) or ligament/pulley (n = 2) rupture were reported in 59 individuals treated with CCH for DC (Table 1). Based on the number of vials distributed and the assumption that 1 vial was used for each injection, the incidence of flexor tendon or ligament/pulley rupture was 0.6 per 1,000 injections. Presuming 1.7 CCH vials per treatment for DC, the mean annual flexor injury (tendon or ligament/pulley rupture) incidence was 0.1% during the overall surveillance period (also 0.1% overall across the surveillance period). Presuming 1.08 CCH vials per treatment for DC, the mean annual incidence was 0.06% ruptures during the surveillance period (0.07% overall across the surveillance period). The incidence of tendon rupture was relatively consistent despite an increase in CCH use over time (Table 2).

The population comprised 29 men, 19 women, and 11 individuals of unidentified sex. For the 36 of 59 cases reporting age, the mean age was 66.5 years (range, 37–80 years). In the identified cases of tendon or ligament rupture, DC was treated in 23 metacarpophalangeal (MCP) joints, 20 proximal interphalangeal (PIP) joints, and 19 unspecified joints in 27 little fingers, 12 ring fingers, 4 middle fingers, 3 index fingers, and 13 unspecified fingers. In the 23 cases for which time-to-rupture details were available, the median time to rupture was 7 days after injection (range, 0–112 days).

Each report of tendon rupture was reviewed by the authors for adherence to the recommended CCH dosing and administration for DC.[2] Four of the 59 cases were associated with inappropriate CCH use related to incorrect dosing of CCH (cases 29, 33, and 54), non–label-adherent injection technique (case 45), off-label use in the thumb (case 33), and/or inappropriate schedule of product administration (dosing scheduled sooner than the recommended 4 weeks, case 29). One reported case of biceps tendon rupture (case 31) was not considered to be related to CCH injection on the basis of the description of the event and the location of the injury. The patient's medical history and concomitant medication use were unknown.

Although the median time to rupture was 7 days, 2 cases of delayed tendon rupture were reported, with a time of onset beyond that anticipated by pharmacodynamics (case 44, 112 days; case 50, 106 days).

Case 44 was a 64-year-old man who received an unknown dose of CCH in the regions of the MCP and PIP joints of his right ring finger for treatment of a 30° MCP contracture with a cord at the palmar base (needle aponeurotomy [NA] performed concomitantly). The patient had no identified medical issues and was not taking other medications. The physician reported a palpable cord present at the time of concomitant CCH injection and NA and that there was no problem associated with injection. The finger extension procedure was performed 1 day later. On day 112, the patient experienced a flexor digitorum superficialis tendon rupture while lifting weights and noted decreased motion because of the injury. The flexor digitorum superficialis rupture was confirmed via physical examination and magnetic resonance imaging, and the physician reported the event as CCH-related.

Case 50 was a 51-year-old man with prior surgical fasciectomy in his left little finger, with subsequent need for secondary flexor tenolysis and tendon repair. Before CCH treatment, the patient had a reported recurrent 65° to 70° contracture of the PIP joint. He received a CCH injection (dose unreported) in a palpable pretendinous cord in the area over the PIP and MCP joints with no injection difficulty. The finger extension procedure was performed 1 day later, after injection of 6 mL of 1% lidocaine, and the patient regained full extension of his finger. On day 106, the patient was seen for complaints of pain and difficulty making a fist. Upon examination, the patient could not flex the PIP or distal interphalangeal joints of this finger, which now also had a 90° PIP contracture. Passively, the distal interphalangeal joint motion was 10° to 30°, and the PIP joint motion was 80° to 100°. The physician diagnosed the patient with flexor digitorum profundus tendon rupture, considered by the physician to be related to CCH, and the patient underwent PIP arthrodesis plus repeat fasciectomy in that finger.

Discussion

Despite a steady annual increase in CCH use in the United States during the 2010–2015 surveillance period, the annual incidence of reported flexor tendon rupture after CCH treatment for DC remained ≤0.1% in this retrospective analysis of postmarketing safety data. On the basis of these data and other available REMS program evidence, the REMS requirement for CCH for the treatment of DC was removed by the US Food and Drug Administration on November 28, 2016.

The rates of flexor tendon rupture in this study (0.10%, presuming 1.7 CCH vials/treatment, or 0.06%, presuming 1.08 CCH vials/treatment) were lower than the rates reported for phase 3 randomized trials and a retrospective chart review of CCH for the treatment of DC. In a 12-month, randomized, double-blind, placebo-controlled trial of CCH treatment, there were no reports of tendon rupture and 1 (1 of 45, 2.2%) report of flexion pulley rupture.[5] A 3-month, randomized, double-blind, placebo-controlled

trial of CCH treatment reported 2 (2 of 204, 1.0%) tendon ruptures.[6] Moreover, a phase 3 open-label trial evaluating treatment using 2 concurrent ("double-dose") injections of CCH (120 treatments total) reported 1 (1 of 60, 1.7%) flexor tendon rupture and 1 (1 of 60, 1.7%) pulley rupture.[14] A retrospective chart review of patients treated with CCH for DC reported 1 (1 of 102, 0.98%) flexor tendon rupture.[16] The incidence was relatively lower in a 1-year surveillance study that collected voluntary AE reports for 115 patients, with a reported tendon rupture rate of 0.37 per 1,000 injections.[10] The lower incidence observed in surveillance studies is likely related to a reliance on spontaneous reporting of AEs.

Flexor tendon rupture is a risk with both NA and treatment with CCH.[8,17] However, tendon complications may be avoided through attention to the prescribing information, which provides specific instructions on how to safely inject CCH into the fascial cord and, importantly, how to avoid the flexor mechanism.[2] The precise depth of injection is important to avoid injecting the flexor tendons, and CCH should be administered slowly and steadily to prevent the liquid from being forced through the cord and into the flexor tendons.[18] Inadvertent deep injection or leakage of CCH below the cord could adversely affect nearby tendons, risking later rupture.[2,3,19]

In this study, other than the cases related to inappropriate CCH dosing or administration technique, the exact cause of tendon rupture in each case was unclear. Several reports of tendon rupture had unusual features, and we could speculate on the mechanism that might explain them. In case 44, in which tendon rupture was reported to have occurred on day 112 after CCH administration, we hypothesize that CCH treatment and concomitant NA might have weakened the tendon, and the high force of weightlifting caused the weakened flexor digitorum superficialis tendon rupture. In case 50, in which tendon rupture was reported on day 102 after CCH administration, we hypothesize that CCH treatment may have weakened the previously repaired tendon. Across the cases of tendon rupture identified in this study, we do not know whether patients may have been taking a medication that increased the risk of tendon rupture (eg, statins, corticosteroids, or fluoroquinolones) or had a comorbidity that increased the tendon rupture risk (eg, diabetes, gout, rheumatoid arthritis, or chronic kidney disease).[20,21] However, in general, the tendon ruptures reported during the surveillance period occurred in a typical population of patients with DC. Namely, because DC most often occurs in the MCP and PIP joints of the ring and little finger, injections in these joint regions are overly represented in the surveillance population.[18]

The present analysis has several limitations. Postmarketing safety data are usually underreported and retrospective in nature, and documentation is frequently incomplete and reliant on spontaneous reporting. Specifically, no information was available on contracture severity prompting CCH treatment; thus, no potential relationship to tendon/pulley injury could be determined. However, there is currently no strong evidence available that the degree of contracture would impact the risk of tendon rupture. Therefore, that information is not likely to have impacted our interpretation of these spontaneously reported cases. This analysis assumed that each vial of CCH distributed under the REMS program for DC was used in treatment (the overall number of injections administered is unavailable). Therefore, the incidence of tendon rupture identified in this analysis may be considered an estimate of the minimum value because it is likely that some cases of rupture were not reported and some vials may have gone unused. Moreover, not all cases noted the use of soft tissue imaging to confirm tendon rupture. Thus, in some cases, a partial tear rather than complete rupture may have occurred (both are reported under the same MedDRA term); hence, the incidence of reported rupture based on MedDRA coding may be imprecise. Although all 57 cases of tendon rupture were coded according to the MedDRA preferred term for this outcome, there were 2 reports of flexor pulley rupture, 1 report of biceps tendon rupture, and 1 report of "bending tendon rupture" according to the verbatim terms. Although these 4 atypical cases were included in the database, we hypothesize that they were likely erroneous reports (owing to internal and/or external reporting errors) and unrelated to CCH treatment. Nonetheless, we used a conservative approach in calculating the rate of tendon rupture and included all types of tendon rupture, regardless of potential reporting errors.

This retrospective pharmacovigilance database analysis is, to the authors' knowledge, the largest assessment of flexor tendon rupture in clinical practice to date, and the results showed that flexor tendon rupture is an infrequent complication of CCH treatment for DC.

Acknowledgments

This study was funded by Endo Pharmaceuticals Inc, Malvern, PA. The sponsor was involved in the study design; the collection, analysis, and interpretation of data; and the decision to submit the article for publication. Medical writing assistance was provided by Heather S. Oliff, PhD, Science Consulting Group, LLC, North Tustin, CA, and editorial assistance was provided by Synchrony Medical Communications, West Chester, PA, under the direction of the authors. Funding for this assistance was provided by Endo Pharmaceuticals Inc, Malvern, PA. Some of these data are available through the US Food and Drug Administration Adverse Event Reporting System (https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis). No additional data will be available from the study sponsor.

References

1. Eberlin KR, Mudgal CS. Complications of treatment for Dupuytren disease. *Hand Clin*. 2018;34(3):387–394.
2. XIAFLEX (collagenase clostridium histolyticum) for injection, for intralesional use. Package insert. Endo Pharmaceuticals Inc; 2021.
3. Schulze SM, Tursi JP. Postapproval clinical experience in the treatment of Dupuytren's contracture with collagenase clostridium histolyticum (CCH): the first 1,000 days. *Hand (N Y)*. 2014;9(4):447–458.
4. Kaplan FT. Collagenase clostridium histolyticum injection for the treatment of Dupuytren's contracture. *Drugs Today (Barc)*. 2011;47(9):653–667.
5. Gilpin D, Coleman S, Hall S, Houston A, Karrasch J, Jones N. Injectable collagenase clostridium histolyticum: a new nonsurgical treatment for Dupuytren's disease. *J Hand Surg Am*. 2010;35(12):2027–2038.e1.
6. Hurst LC, Badalamente MA, Hentz VR, et al. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med*. 2009;361(10):968–979.
7. Peimer CA, Blazar P, Coleman S, Kaplan FT, Smith T, Lindau T. Dupuytren contracture recurrence following treatment with collagenase clostridium histolyticum (CORDLESS [Collagenase Option for Reduction of Dupuytren Long-term Evaluation of Safety Study]): 5-year data. *J Hand Surg Am*. 2015;40(8):1597–1605.
8. Fletcher J, Tan ESL, Thomas M, Taylor F, Elliott D, Bindra R. Collagenase injections for Dupuytren's contracture: prospective cohort study in a public health setting. *ANZ J Surg*. 2019;89(5):573–577.
9. Nayar SK, Pfisterer D, Ingari JV. Collagenase clostridium histolyticum injection for Dupuytren contracture: 2-year follow-up. *Clin Orthop Surg*. 2019;11(3):332–336.
10. Peimer CA, McGoldrick CA, Fiore GJ. Nonsurgical treatment of Dupuytren's contracture: 1-year US post-marketing safety data for collagenase clostridium histolyticum. *Hand (N Y)*. 2012;7(2):143–146.
11. Zhang D, Earp BE, Blazar P. Risk factors for skin tearing in collagenase treatment of Dupuytren contractures. *J Hand Surg Am*. 2019;44(12):1021–1025.
12. Wei DH, Cantlon MB, Wakefield DB, Vitale MA. Risk factors for skin tears following collagenase clostridium histolyticum to treat Dupuytren contractures. *J Hand Surg Am*. 2020;45(10):989.e1–989.e10.
13. Fagernæs C, Mallet S. The risk of skin tear in Dupuytren's disease when treated with collagenase. *Dan Med J*. 2018;65(5):A5478.
14. Coleman S, Gilpin D, Kaplan FT, et al. Efficacy and safety of concurrent collagenase clostridium histolyticum injections for multiple Dupuytren contractures. *J Hand Surg Am*. 2014;39(1):57–64.
15. Peimer CA, Skodny P, Mackowiak JI. Collagenase clostridium histolyticum for Dupuytren contracture: patterns of use and effectiveness in clinical practice. *J Hand Surg Am*. 2013;38(12):2370–2376.

16. McMahon HA, Bachoura A, Jacoby SM, Zelouf DS, Culp RW, Osterman AL. Examining the efficacy and maintenance of contracture correction after collagenase clostridium histolyticum treatment for Dupuytren's disease. *Hand (N Y)*. 2013;8(3):261–266.
17. Beaudreuil J, Lellouche H, Orcel P, Bardin T. Needle aponeurotomy in Dupuytren's disease. *Joint Bone Spine*. 2012;79(1):13–16.
18. Brazzelli M, Cruickshank M, Tassie E, et al. Collagenase clostridium histolyticum for the treatment of Dupuytren's contracture: systematic review and economic evaluation. *Health Technol Assess*. 2015;19(90):1–202.
19. Khurana S, Wadhwa V, Chhabra A, Amirlak B. MRI in flexor tendon rupture after collagenase injection. *Skeletal Radiol*. 2017;46(2):237–240.
20. Murray PM. Flexor tendon ruptures in the rheumatoid patient. *Oper Tech Orthop*. 1998;8(2):92–97.
21. Deren ME, Klinge SA, Mukand NH, Mukand JA. Tendinopathy and tendon rupture associated with statins. *JBJS Rev*. 2016;4(5):e4.