

Multiple Collagenase Injections Are Safe for Treatment of Dupuytren's Contractures

VARUN K. GAJENDRAN, MD; VINCENT HENTZ, MD; DEBORAH KENNEY, MS; CATHERINE M. CURTIN, MD

abstract

Full article available online at Healio.com/Orthopedics

The authors report the case of a 65-year-old, right-hand-dominant man who had severe Dupuytren's disease with multiple cords and flexion contractures of the metacarpophalangeal and proximal interphalangeal joints of both hands and underwent repeated collagenase injections for treatment. Collagenase has been shown to be safe and effective in the treatment of Dupuytren's contractures when administered as a single dose, but the results of multiple injections over a prolonged period are unknown. Antibodies to collagenase develop in all patients after several treatments, raising concerns about safety and efficacy as a result of sensitization from repeated exposures. The antibodies generated as a result of repeated exposure to collagenase could theoretically render it less effective with time and could also lead to immune reactions as severe as anaphylaxis. The authors present the case of a single patient who experienced continued correction of his contractures with only minor and self-limited adverse reactions after administration of 12 collagenase doses through 15 injections during a 4-year period. Over time, the injections continued to be effective at correcting metacarpophalangeal joint contractures, but less effective at correcting proximal interphalangeal joint contractures. The patient did eventually require a fasciectomy, but the safety and modest success of the repeated collagenase injections shows promise for a less invasive treatment with a better risk profile than open fasciectomy. Although further studies are needed, repeated administration of collagenase appears to be safe and modestly effective for severe Dupuytren's contractures, although a fasciectomy may ultimately be required in the most severe cases.

The authors are from the Department of Orthopaedic Surgery (VKG) and the Division of Plastic Surgery (VH, DK, CMC), Stanford University, Robert A. Chase Center for Hand and Upper Limb Surgery, Stanford University Hospitals and Clinics, Redwood City, California.

Dr Gajendran and Ms Kenney have no relevant financial relationships to disclose. Dr Hentz is a Scientific Advisory Board Member for Auxilium Pharmaceuticals and a recipient of consulting fees. Dr Curtin received compensation for participation in the phase III clinical trial of collagenase.

Correspondence should be addressed to: Varun K. Gajendran, MD, Department of Orthopaedic Surgery, Stanford University, Robert A. Chase Center for Hand and Upper Limb Surgery, Stanford University Hospitals and Clinics, 450 Broadway St, MC 6342, Pavilion A, 2nd Floor, Dept A26, Redwood City, CA 94063 (varun182@stanford.edu).

Received: August 25, 2013; Accepted: December 27, 2013; Posted: July 11, 2014.

doi: 10.3928/01477447-20140626-64

Dupuytren's disease is a genetic disorder that can lead to disabling digital flexion contractures, and surgical excision has been the mainstay of treatment for severe cases.¹⁻⁴ Despite excellent results, surgery has well-established risks, including infection, problems with wound healing, digital nerve and arterial injury, and complex regional pain syndrome.^{1,3-5} Patients with severe disease can have multiple recurrences and require revision surgeries that are even more technically demanding, with higher complication rates.^{2,3} Therefore, nonoperative treatment is attractive for these patients.

Collagenase is a nonoperative treatment option for Dupuytren's disease and uses 2 enzymes derived from *Clostridium histolyticum* to lyse and weaken the abundant collagen in the diseased cords.^{1,3,6-14} Currently, collagenase can only be injected into 1 cord at a time. Therefore, patients with severe disease involving multiple cords require multiple visits. There are concerns about repeated injections because nearly all patients form antibodies against collagenase after the first injection.¹¹ The clinical significance of this immune response after repeated injections remains unclear. The effectiveness of the enzymes after repeated injections is also unknown. There are theoretical concerns that repeated injections may prime the immune system and result in major systemic reactions or potentially reduce the effectiveness of the drug. This case report presents a single patient who received 12 doses through 15 injections of collagenase over a 4-year period for flexion contractures from Dupuytren's disease.

CASE REPORT

The patient is a 65-year-old, right-hand-dominant man with severe Dupuytren's disease with involvement of multiple cords, causing flexion contractures of the metacarpophalangeal and proximal interphalangeal joints of both hands. He was enrolled in a phase III collagenase

Table 1			
Collagenase Injections			
Date of Injection	Site of Injection	Preinjection Contracture	Postinjection Contracture
Phase III trial injections			
12/2007	Right small finger PIP	50°	5°
1/2008	Right ring finger MCP	20°	0°
2/2008	Left ring finger PIP	40°	35°
3/2008	Left small finger PIP	35°	20°
4/2008	Left small finger PIP	20°	10°
5/2008	Right small finger PIP	30°	20°
6/2008	Right ring finger MCP	20°	0°
Outside hospital injections			
1/2011	Right small finger MCP	25°	0°
2/2011	Right small finger PIP	55°	55°
4/2011	Right small finger PIP	55°	35°
6/2011	Right small finger PIP	40°	N/A ^a
11/2011	Left ring finger MCP	20°	0°
12/2011 ^b	Right small finger MCP	15°	0°
12/2011 ^b	Right ring finger MCP	15°	0°
12/2011 ^b	Right long finger MCP	15°	0°

Abbreviations: MCP, metacarpophalangeal joint; N/A, not available; PIP, proximal interphalangeal joint.

^aPatient underwent partial palmar fasciectomy of the right small finger for proximal interphalangeal joint contracture in August 2011.

^bIn December 2011, 1 dose of collagenase was divided and injected into 3 separate cords.

trial in 2007 and received 7 injections as part of that trial. After the trial injections, the patient had swelling, ecchymoses, and pruritus in the hands, but these adverse events were of similar intensity after all 7 injections.

After completion of the phase III trial, the patient continued to have contractures and sought additional collagenase treatments with a hand surgeon at an outside facility. He had 8 additional collagenase injections (3 injections were 1 dose of collagenase divided into 3 cords) as well as needle aponeurotomy performed by the outside hand surgeon. The patient continued follow-up with the authors as part of the longitudinal arm of the original collagenase study. At these annual follow-up visits, the authors examined the patient's hands and obtained a history and docu-

mentation of additional treatments that he had received at the outside facility.

A complete listing of all of the collagenase injections that the patient received is shown in **Table 1**. Data from the annual follow-up visits for each contracture are shown in **Table 2**. After completion of the phase III trial, the patient had recurrences and progression of the contractures of the right small finger proximal interphalangeal and metacarpophalangeal joints, as seen in the January 2011 follow-up data (55° and 25°, respectively). Although he had several additional injections of collagenase in the small finger for proximal interphalangeal joint contracture, he ultimately required a fasciectomy, which improved the contractures, as noted during the February 2012 evaluation (15° and 0° for the proximal interphalangeal and

metacarpophalangeal joints, respectively). Throughout the 4-year period during which the patient received 15 collagenase injections, he reported no changes in the quality and intensity of the reactions after injection. The patient was appropriately counseled that the division of a single dose of collagenase into multiple cord injections at a single visit was off-label use and could potentially lead to unknown adverse reactions. However, he was pleased with the results of the previous collagenase injections and consented to proceed after accepting the risks.

DISCUSSION

Surgery is often performed for moderate to severe Dupuytren's disease, but surgery can be problematic for those with the most severe disease. These patients often require revision surgeries that have a substantially higher risk of complications.² Thus, for those with the most severe disease, a less invasive option is appealing.

Collagenase injection is a minimally invasive treatment for Dupuytren's contracture that has been proven effective and safe; serious complications are rare.^{1,8,11} A recent long-term follow-up of 8 patients who were treated with collagenase injections found recurrence of contractures, but the recurrent metacarpophalangeal joint contractures were less severe at 8 years vs preinjection, and none of the patients required further surgery.¹⁴ For patients with severe disease, collagenase treatment would likely require multiple injections, as seen in the current patient. Repeated exposure to the drug resulted in the formation of antibodies. In the first randomized, controlled collagenase trial (in which the current patient was a subject), 86% of patients were noted to have antibodies to 1 or both types of collagenase after the first injection and all patients had antibodies to both types of collagenase after the third injection.¹¹ These antibodies could theoretically lead to immunoresistance or hypersensitivity.¹⁵

Botulinum toxin (Botox) is a similar medication with large proteins that can be

Table 2

Annual Follow-up of Digital Range of Motion for up to 4 years				
Finger and Joint	Contracture at Follow-up in January 2009	Contracture at Follow-up in January 2010	Contracture at Follow-up in January 2011	Contracture at Follow-up in February 2012
Right small finger PIP	5°	30°	40° ^a	15°
Right small finger MCP	0°	10°	10°	0°
Right ring finger PIP	0°	10°	15°	15°
Right ring finger MCP	0°	10°	10° ^b	0°
Left small finger PIP	15°	25°	30°	40°
Left small finger MCP	0°	0°	0°	0°
Left ring finger PIP	0°	30°	25°	10°
Left ring finger MCP	0°	10°	0°	0°

Abbreviations: MCP, metacarpophalangeal joint; PIP, proximal interphalangeal joint.
^aPatient underwent partial palmar fasciectomy in August 2011.
^bPatient underwent needle aponeurotomy in July 2011.

serially injected, and it has a long history with a well-researched safety profile. The original botulinum toxin formulations resulted in the formation of blocking antibodies in some patients, decreasing the clinical response to the medication with repeated use. The formulation of botulinum toxin has since been refined over the years to overcome this limitation.^{16,17} It is not yet known whether blocking antibodies can occur with collagenase, but the current patient continued to show improvement in his contractures, even after the last injection. Although the results of multiple collagenase injections in this case were less favorable for proximal interphalangeal joint contractures compared with metacarpophalangeal joint contractures, this is consistent with the results obtained in the phase III trial.¹¹ It is also comparable to the results of surgical treatment in that proximal interphalangeal joint contractures have significantly worse outcomes and higher rates of complications compared with metacarpophalangeal joint contractures after partial fasciectomy.² Future studies are needed to formally assess the efficacy of collagenase with repeated injections and compare its results with those of surgical treatment,

particularly for the challenging proximal interphalangeal joint contracture.

Another concern with multiple injections is the possibility of a hypersensitivity reaction. Again considering botulinum toxin, there have been documented cases of hypersensitivity and anaphylaxis.¹⁸ However, these are rare, with large series showing no increase in severe adverse effects after repeated treatments administered over the long term. A large meta-analysis of 36 studies that included 1425 patients receiving botulinum toxin found no severe adverse reactions, with a 25% rate of mild to moderate adverse reactions compared with 15% in the control group; focal weakness was the only adverse event that occurred more frequently in the botulinum toxin group.^{19,20} In the second randomized, controlled collagenase trial, only 3 of the 1082 patients who received 2 or more injections had clinically significant urticaria, and all 3 cases resolved uneventfully with oral medications.⁸ There are no reports to date of systemic reactions such as anaphylaxis, and the current patient noted no changes in the already mild adverse effects with later injections. As with botulinum toxin, however, larger-scale studies of patients receiving repeated injections over the long term

are needed to fully characterize the safety profile of collagenase.

CONCLUSION

In conclusion, the authors reported the case of a single patient who received 12 doses through 15 collagenase injections for severe Dupuytren's disease over a 4-year period. The patient had continued correction of contractures without major adverse reactions. Although he had antibodies to both types of collagenase after the first 3 injections, his primed immune response did not lead to serious adverse reactions or mitigate the effectiveness of the later injections. Further studies with a larger cohort will be useful to confirm the safety and efficacy of collagenase after repeated injections, but the results from this case are encouraging.

REFERENCES

- Black EM, Blazar PE. Dupuytren disease: an evolving understanding of an age-old disease. *J Am Acad Orthop Surg*. 2011; 19(12):746-757.
- Coert JH, Nérin JP, Meek MF. Results of partial fasciectomy for Dupuytren disease in 261 consecutive patients. *Ann Plast Surg*. 2006; 57(1):13-17.
- Desai SS, Hentz VR. The treatment of Dupuytren disease. *J Hand Surg Am*. 2011; 36(5):936-942.
- Stanbury SJ, Hammert WC. Dupuytren contracture. *J Hand Surg Am*. 2011; 36(12):2038-2040.
- Worrell M. Dupuytren's disease. *Orthopedics*. 2012; 35(1):52-60.
- Badalamente MA, Hurst LC, Hentz VR. Collagen as a clinical target: nonoperative treatment of Dupuytren's disease. *J Hand Surg Am*. 2002; 27(5):788-798.
- Desai SS, Hentz VR. Collagenase *Clostridium histolyticum* for Dupuytren's contracture. *Expert Opin Biol Ther*. 2010; 10(9):1395-1404.
- 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.
- Holzer LA, Holzer G. Collagenase *Clostridium histolyticum* in the management of Dupuytren's contracture. *Handchir Mikrochir Plast Chir*. 2011; 43(5):269-274.
- Hurst LC, Badalamente MA. Nonoperative treatment of Dupuytren's disease. *Hand Clin*. 1999; 15(1):97-107, vii.
- 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.
- Kaplan FT. Collagenase *Clostridium histolyticum* injection for the treatment of Dupuytren's contracture. *Drugs Today (Barc)*. 2011; 47(9):653-667.
- Srinivasan RC, Shah AS, Jebson PJ. New treatment options for Dupuytren's surgery: collagenase and percutaneous aponeurotomy. *J Hand Surg Am*. 2010; 35(8):1362-1364.
- Watt AJ, Curtin CM, Hentz VR. Collagenase injection as nonsurgical treatment of Dupuytren's disease: 8-year follow-up. *J Hand Surg Am*. 2010; 35(4):534-539.e1.
- Edkins TJ, Koller-Eichhorn R, Alhadeff JA, Mayer U, Faust H, Del Tito BJ. Assessment of potential cross-reactivity of human endogenous matrix metalloproteinases with collagenase *Clostridium histolyticum* antibodies in human sera obtained from patients with Dupuytren's contracture. *Clin Vaccine Immunol*. 2012; 19(4):562-569.
- Göschel H, Wohlfarth K, Frevert J, Dengler R, Bigalke H. Botulinum A toxin therapy: neutralizing and nonneutralizing antibodies—therapeutic consequences. *Exp Neurol*. 1997; 147(1):96-102.
- Klein AW. Complications and adverse reactions with the use of botulinum toxin. *Semin Cutan Med Surg*. 2001; 20(2):109-120.
- Li M, Goldberger BA, Hopkins C. Fatal case of BOTOX-related anaphylaxis? *J Forensic Sci*. 2005; 50(1):169-172.
- Naumann M, Albanese A, Heinen F, Molenaers G, Relja M. Safety and efficacy of botulinum toxin type A following long-term use. *Eur J Neurol*. 2006; 13(suppl 4):35-40.
- Naumann M, Jankovic J. Safety of botulinum toxin type A: a systematic review and meta-analysis. *Curr Med Res Opin*. 2004; 20(7):981-990.