

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Hurst LC, Badalamente MA, Hentz VR, et al. Injectable collagenase clostridium histolyticum for Dupuytren's contracture. *N Engl J Med* 2009;361:968-79.

Injectable Collagenase Clostridium Histolyticum for Dupuytren's Contracture

Lawrence C. Hurst, M.D., Marie A. Badalamente, Ph.D., Vincent R. Hentz, M.D., Robert N. Hotchkiss, M.D., F. Thomas D. Kaplan, M.D., Roy A. Meals, M.D., Theodore M. Smith, Ph.D., and John Rodzvilla, M.D., for the CORD I Study Group

Appendix

Members of the Collagenase Option for Reduction of Dupuytren's (CORD) I Study Group were Edward Akelman, M.D. (Rhode Island Hospital, Providence, RI); Brian Bear, M.D. (Rockford Orthopedic Associates, Ltd., Rockford, IL); Mark R. Belsky, M.D. (Newton-Wellesley Hospital, Newton, MA); Philip Blazar, M.D. (Brigham and Women's Hospital, Boston, MA); Eric N. Britton, M.D. (Hand Surgery Associates, Denver, CO); Bronier Costas, M.D. (The Hand and Upper Extremity Center of Georgia, P.C., Atlanta, GA); Joel L. Frazier, M.D. (Health Research Institute, Oklahoma City, OK); Vincent Hentz, M.D. (Stanford Hospital and Clinics, Palo Alto, CA); Robert N. Hotchkiss, M.D. (Hospital for Special Surgery, New York, NY); Lawrence C. Hurst, M.D. and Marie A. Badalamente, Ph.D. (SUNY at Stony Brook, Department of Orthopaedics, Stony Brook, NY); F. Thomas D. Kaplan, M.D. (The Indiana Hand Center, Indianapolis, IN); John Lubahn, M.D. (Hand Microsurgery and Reconstructive Orthopaedics, Erie, PA); Scott McPherson, M.D. (TRIA Orthopaedic Center, Minneapolis, MN); Roy Meals, M.D. (Private Practice, Los Angeles, CA); Clayton A. Peimer, M.D. (Marquette General Health System, Marquette, MI); and Douglas Roesht, M.D. (University Orthopedics Center, State College, PA).

Injection Technique

Before injection of collagenase clostridium histolyticum, the affected cord was carefully palpated under tension. Injection occurred where the cord was maximally separated from the underlying flexor tendons, usually at a point of maximum “bowstringing” of the cord and where the skin was not intimately adhered to the cord. After reconstitution of the study drug, the skin was prepared with a suitable antiseptic (e.g., betadine, isopropyl alcohol, or both) and wiped dry with sterile gauze. The needle was placed through the skin and into the cord (but not through it). If the patient had a Y-shaped natatory cord, the “point” of the Y was injected. A small amount of gentle passive motion at the distal interphalangeal joint helped confirm proper needle placement. Once the needle was in the middle of the cord, approximately one-third of the volume was injected. The needle was partially withdrawn and replaced in a slightly more distal position in the affected cord and another one-third of the volume was injected. Finally, the needle was partially withdrawn and repositioned proximal to the initial injection site and the remaining volume was injected. An alternative procedure was also used: approximately one-third of the volume was injected, the needle was completely withdrawn, another one-third of the volume was injected into a second site approximately 1-2 mm distally, the needle was completely withdrawn, and the final one-third of the volume was injected into a third injection site. After reports of tendon rupture, investigators were reminded, for injection of proximal interphalangeal joints in the little finger, to avoid injecting more than 4 mm distal to the palmar digital crease, not to inject more than 2 to 3 mm in depth, and inject as far proximally from the proximal interphalangeal joint as possible.

Standardized Manipulation Technique

Twenty-four hours after injection, patients visited investigators’ offices for follow-up as an outpatient. Investigators performed standard passive extension at the first follow-up visit.

Investigators applied moderate pressure while patients’ wrists were flexed to produce extension of the finger. The force of extension was persistent and to the extent of the patients’ pain tolerance. Passive extension of the finger beyond the patients’ pain threshold was unadvised. Finger extension was sustained for approximately 10 to 20 seconds. When manipulating the proximal interphalangeal joint, the metacarpophalangeal was kept flexed. If the first extension attempt did not rupture the cord, second and third attempts could be performed, allowing an interval of 5 to 10 minutes between each manipulation. After three attempts, no further extension of the finger was performed. Obtaining complete rupture at the first return visit was helpful but not necessary. Direct pressure on the injection site was avoided because of tenderness.

Sample Size Determination

Table 1. Sample Size Calculation for Each Joint Type.

Joint	Response Rate Active vs Placebo	Sample Size Active/Placebo
Metacarpophalangeal	80% vs 10%	14/7
Proximal Interphalangeal	70% vs 10%	18/9

To adequately assess safety, 216 patients were needed: 144 with metacarpophalangeal joint contractures and 72 proximal interphalangeal joint contractures. Patients were randomized with a centralized interactive voice response system to active treatment or placebo with a ratio of 2:1 in favor of the active treatment within each joint type/baseline severity strata. Equal allocation to treatment groups was deemed unnecessary because of the anticipated high rate of clinical success.

Safety Data

Immunogenicity

A validated enzyme-linked immunogenicity assay was used to detect the presence of antibodies against clostridial type I collagenase (AUX-I), clostridial type II collagenase (AUX-II), or both, in serum samples that were collected at screening and 30 days after each injection. If antibodies were detected, titers were quantified using a titer determination assay. Most patients ($\geq 85.8\%$) tested positive for antibodies against collagenase 30 days after the first injection. Among patients who received 3 injections, all tested positive for antibodies to collagenase clostridium histolyticum. No patients reported an adverse event that was indicative of a significant systemic allergic response to collagenase clostridium histolyticum.

Severe Treatment-Related Adverse Events

Table 2. Patients With ≥ 1 Severe Treatment-related Adverse Event.*

Variable	Collagenase (N = 204)	Placebo (N = 104)
	<i>no. of patients (%)</i>	
Patients with ≥ 1 severe treatment-related adverse event, n (%)	20 (9.8)	2 (1.9)
Peripheral edema	4 (2.0)	0
Injection-site pain	4 (2.0)	0
Upper-extremity pain	4 (2.0)	0
Injection-site hemorrhage	3 (1.5)	0
Contusion	2 (1.0)	0
Tenderness	2 (1.0)	0
Chest-wall pain	1 (0.5)	0
Contact dermatitis	1 (0.5) [‡]	0
Ecchymosis	1 (0.5)	0
Injection-site cellulitis	1 (0.5)	0
Muscle spasms	1 (0.5) [‡]	0
Myocardial infarction [†]	1 (0.5) [‡]	0
Skin laceration	1 (0.5)	0
Tendon rupture ^{†§}	1 (0.5)	0
Acute cholecystitis [†]	0	1 (1.0) [‡]
Nasopharyngitis	0	1 (1.0) [‡]
Radius fracture	0	1 (1.0) [‡]

*Treatment-related adverse events had a possible, probable, or missing relationship to study drug.

†This event was a serious adverse event.

‡This event was deemed by investigator to be unrelated to study drug.

§Two tendon ruptures occurred after treatment with collagenase clostridium histolyticum. The first rupture, which was moderate in intensity, was diagnosed 8 days after the first injection into the proximal interphalangeal joint of the little (fifth) finger. Magnetic resonance imaging (MRI) showed a full tear of the flexor digitorum profundus and a partial tear of the flexor digitorum superficialis. Treatment was excision of the flexor digitorum profundus and tenolysis of the flexor digitorum superficialis, followed by physical therapy. The second rupture, which was severe in intensity, was diagnosed 8 days after the third injection into the little (fifth) finger. The metacarpophalangeal joint received two injections and the proximal interphalangeal joint received one injection. Confirmation of a full tear of the flexor digitorum profundus and flexor digitorum superficialis occurred at surgery. Treatment was excision of the flexor digitorum profundus and flexor digitorum superficialis and placement of a Hunter rod, followed by hand therapy. The second stage of treatment was transplantation of tendon into the flexor digitorum profundus.