Collagenase Total Occlusion-1 (CTO-1) Trial
A Phase I, Dose-Escalation, Safety Study

Bradley H. Strauss, MD, PhD; Azriel B. Osherov, MD; Sam Radhakrishnan, MD; G.B. John Mancini, MD; Allison Manners, BSc; John D. Sparkes, MSc; Robert J. Chisholm, MD

Background—Percutaneous interventions for chronic total occlusions have low success rates, primarily because of failure of guide wire crossing. Collagen-rich matrix constitutes the main barrier to chronic total occlusion crossing. In preclinical studies, local delivery of a bacterial collagenase formulation improved guide wire crossing. The Collagenase Total Occlusion-1 (CTO-1) Trial is a phase I, dose-escalation trial to assess the safety and efficacy of collagenase therapy to facilitate guide wire crossing in coronary artery chronic occlusions.

Methods and Results—Twenty subjects with ≥1 previous failure of chronic total occlusion guide wire crossing were enrolled at 2 sites. Subjects were treated in 4 distinct cohorts of 5 patients, with escalation of collagenase dose in each cohort from 300 to 1200 μg. Collagenase was locally delivered into the occlusions with either an over-the-wire balloon system (n=8) or a fine-cross microcatheter (n=12) for a period of 30 minutes. Subjects were brought back to the catheterization laboratory for guide wire crossing and angioplasty the next day. Guide wire crossing was successfully achieved in 15 subjects (75%). A soft-tip guide wire (Whisper, Pilot-50, Fielder XT) was either the sole or predominant guide wire used in 75% of successful crossings. Non–ST-segment–elevation myocardial infarctions occurred in 3 patients as a result of side-branch ischemia during stenting. Computed tomographic angiography at 3 months showed no late complications and patent stents in successfully treated chronic total occlusion. Anginal improvement occurred with a reduction in Canadian Cardiovascular Society class from baseline to 3 months (2.5±0.6 versus 0.9±0.9; \(P<0.001\)).

Conclusion—Local delivery of collagenase into coronary chronic total occlusion is feasible and safe with encouraging guide wire crossing results in previously failed cases. Larger clinical trials are required to determine efficacy.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01271335.

(Circulation. 2012;125:522-528.)

Key Words: angioplasty ■ collagenases ■ coronary artery disease ■ occlusions ■ metalloproteinases

Success rates of percutaneous coronary interventions (PCIs) in chronic total occlusions (CTOs) have been suboptimal, in the range of 55% to 80%.1–4 Data from the National Cardiovascular Data Registry showed that PCI attempt rates for chronic occlusions in the United States remain low, in the range of 12%, and have not changed over the past 5 years despite advances in techniques and technology.5,6 The main reason for failure is the inability to cross the CTO with a guide wire. Preclinical model studies and human autopsy studies have shown that collagen is the predominant component in the occluded lesions and acts as occlusive barrier at the proximal fibrous cap.7–9 Collagenase, a matrix metalloproteinase enzyme that selectively degrades type I collagen, has been shown to facilitate guide wire crossing in an animal model of CTO.10,11 The objectives of this study were to assess the feasibility, safety, and efficacy of locally delivering collagenase into chronic occlusions to facilitate guide wire crossing in patients with at least 1 previously failed attempt to revascularize CTO.

Clinical Perspective on p 528

Methods

The trial was designed as a prospective, 2 center, open-label, phase I safety and tolerability, single-ascending-dose study. The trial was approved by Health Canada and the Institutional Research Ethics Board at the 2 participating sites.

All subjects provided written informed consent before participation in the trial. Study subjects were enrolled in 4 discrete dosing cohorts, with escalation of collagenase (referred to as MZ-004) dose with each cohort (300, 600, 900, and 1200 μg). Five subjects were enrolled in each dose cohort. All eligible subjects must have had at least 1 previous failed attempt of percutaneous revascularization of the CTO. Collagenase dose escalation was done on the recommen-
ation of an independent Data and Safety Monitoring Board (DSMB) after angiographic and clinical review of each trial subject within the previous dose cohort and in accordance with a written and approved DSMB charter. The trial subjects were screened for inclusion and exclusion criteria before being eligible to be treated in a 2-stage procedure. Once screened, the trial subjects were brought into the hospital, and the collagenase injection was performed on day 0. Subjects were monitored overnight in a holding bay and returned to the catheterization laboratory on day 1 for the PCI attempt. Subjects underwent 2-dimensional echocardiographic studies for assessment of left ventricular function and pericardial effusions on day 1 after collagenase injection before the PCI procedure and again on day 2 before discharge. A follow-up computed tomographic (CT) coronary angiogram was performed at 3 months to assess for any pericardial/myocardial changes and the patency of the stents. In the first dose cohort, occlusion duration (when known) was ≤2 years. However, for the second to fourth dose cohorts, there was no CTO age restriction; this protocol amendment was approved by each center’s Research Ethics Board and Health Canada.

Patients eligible for inclusion included male or female subjects >35 years of age with a known chronic occlusion of >6 weeks’ duration or absence of ischemic event in the 6 weeks before enrollment or in subjects with CTO of unknown duration with a clinical indication for revascularization, at least 1 failed attempt to cross the occlusion, and the absence of pericardial effusion on a 2-dimensional echocardiogram. Main exclusion criteria included saphenous vein graft occlusion, ostial coronary occlusion, renal dysfunction (creatinine >2 times the upper limit of normal), pregnancy, or recent (within 6 weeks) acute coronary syndrome.

The primary outcome of the study was to evaluate the safety and tolerability of acute intracoronary doses of collagenase (MZ-004). The primary outcome of the study was the frequency, severity, and relatedness of cardiac adverse events (AEs) and serious AEs (SAEs) reported during the treatment and follow-up phases. An AE was defined as any untoward medical occurrence that a subject experienced while involved in the clinical investigative study (expected or unexpected) that may or may not have a causal relationship with this treatment. An SAE was defined as any untoward medical occurrence during the conduct of the study that resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability. The safety and tolerability of the treatment during the treatment period were assessed by serial cardiac enzymes at 6 and 18 hours after the procedures and the presence of pericardial effusions and again at 3 months when subjects underwent a CT coronary angiogram to assess for delayed vascular and myocardial effects. A pericardial effusion >1 cm or any echocardiographic signs of tamponade on day 1 were a contraindication to performing the PCI revascularization procedure.

The secondary end point was guide wire crossing success. Because this was the first experience with using collagenase in human coronary CTO cases, it was determined a priori that a success rate in any cohort of ≥30% (ie, at least 2 of the 5 patients in that specific cohort successfully crossed with a guide wire) would suggest the possibility of a beneficial clinical effect and would support further clinical testing of MZ-004 at that dose in future studies.

Angiographic images were quantitatively analyzed before and after PCI with previously described and validated software at the Cardiovascular Imaging Research Core Laboratory, University of British Columbia, Vancouver, BC, Canada (director, G.B.J.M.).12,13

The pre-PCI angiogram was used to determine occlusion length and for qualitative assessments, including stump morphology (blunt or tapered), presence of bridging collaterals, and location of branches relative to the CTO.

Details of Collagenase

MZ-004 is a proprietary bacterial collagenase formulation manufactured in the United States for Matrizyme Pharma under good manufacturing practices conditions. This form of collagenase is a mixture of several isoforms of collagenase, primarily isoform IA and II. MZ-004 is produced from the fermentation of the Clostridium histolyticum bacterium, which has been chromatographically purified (and therefore is appropriate for clinical use) and shown to be active by 2 individual enzymatic activity assays, collagen digestion and furylacryloyl-leucine-glycyl-propyl-alanine hydrolysis. The fermentation product also contains small amounts (≤1 U/mg protein) of additional proteolytic enzymes, including neutral proteases and elastase, which are controlled to approved specifications to produce a high-activity formulation. MZ-004 has had the neutral proteases (caselnases) removed.

C. histolyticum collagenase was selected for use over mammalian and human collagenases because it is more efficient at breaking down different types of collagen in the body. Human collagenase tends to cleave type I collagen at a point called the 3/4 position of the molecule and is capable of cleaving all 3 strands in the helix at this 1 locus, leaving 2 segments, one 71 kDa and the other 24 kDa, both of which can be further digested by trypsin and other nonspecific proteases.14,15 Bacterial collagenase derived from C. histolyticum has been well characterized and has been shown to be extremely effective at degrading all types of collagen. It is able to cleave collagen molecules predominantly at sequences that include GLY-PRO-X-GLY-PRO-Y, with cleavage occurring between the X-GLY component, where X and Y represent any amino acid.16 This sequence is very common in collagen molecules, allowing scission into numerous small polypeptide chains. This allows complete and rapid digestion of collagen without the aid of other proteases, making it very attractive for use in therapeutic applications when collagen is to be degraded with exogenous delivery of collagenase.

MZ-004 (lot 059K7250; collagen digestion, 1148 U/mg solid; furylacryloyl-leucine-glycyl-propyl-alanine, 8.8 U/mg solid) was supplied in individual 2-mL type I glass vials as a lyophilized/sterile powder stored at 80°C. On the day of dosing, 1 vial of lyophilized MZ-004 was removed from the freezer and thawed at room temperature for 15 to 20 minutes. The entire vial of MZ-004 (2 mg) was diluted with sterile 0.9% normal saline (United States Pharmacopeia). Subsequent dilutions with sterile 0.9% normal saline were necessary to arrive at the specific cohort dose level. Once the correct dose had been achieved, the solution was filtered through a 0.2-μm disk filter into a sterile vial and then drawn up into the individual subject’s syringe and labeled accordingly, ready for subject administration.

Collagenase Administration

Collagenase was injected locally into the occlusion through either a 2.0-mm diameter over-the-wire (OTW) angioplasty catheter (n=8 patients; Voyageur, Abbott Vascular) or a fine-cross microcatheter (n=12 patients; Terumo). In the initial cases, the OTW angioplasty catheter was advanced under fluoroscopic guidance into the coronary artery immediately proximal to the CTO. The balloon was inflated to 4 atm to prevent proximal runoff of the infusate. The guide wire was removed, and the solution containing collagenase was administered over 15 minutes through the wire port and then flushed with 0.3 mL of saline over 5 minutes. Overall, the balloon was inflated for 30 minutes. During the second dosing cohort, it became apparent in some cases that the OTW catheter could not be advanced close enough to the occlusion owing to tortuosity of the coronary artery. Thus, the collagenase delivery protocol was changed to a fine-cross catheter positioned directly into the CTO over a guide wire that was advanced a short distance (first 2–3 mm) into the occlusion. The collagenase formulation was injected slowly over 15 minutes and flushed with 0.3 mL saline over 5 minutes. The catheter was left in place for an additional 10 minutes. After balloon deflation or removal of the fine-cross catheter, a final contrast injection was done to assess for dissections in the artery proximal to the occlusion or in the CTO itself.

The coronary percutaneous revascularization attempt was done 18 to 24 hours after administration of the collagenase with standard techniques and equipment. Types of guide wires, fluorescence time, procedure times, and contrast volumes were recorded.

For the collagenase injection procedure, it was not necessary to visualize the distal lumen by collaterals through dual coronary artery contrast angiograms because the injection was limited to the first 2
to 3 mm of the occlusion. However, during the attempt to cross the occlusion the next day, it was always necessary to properly visualize the distal lumen to ensure a safe guide wire crossing. This often necessitated dual coronary artery angiograms. Anticoagulation for all procedures was done with heparin alone with a target activated clotting time of $\leq 250$ s for the collagenase injection procedure and $\leq 300$ s for the PCI procedure. An example of the stages of the procedure, including positioning of the fine-cross microcatheter for the CTO injection, is shown in the Figure.

### Statistical Analysis

Results are reported as the 50th percentile (median) and as the 25th (quartile 1 [Q1]) and 75th (quartile 3 [Q3]) percentiles, except for ejection fraction, Canadian Cardiovascular Society (CCS) angina class, CTO age, and number and length of stents, which are reported as mean ± SD. No formal sample size justification for efficacy was performed because this was a dose-finding safety, phase I study. Changes in CCS angina score were compared by use of a paired Student $t$ test that compared the average change in CCS score with no change. A value of $P<0.05$ was considered statistically significant.

### Results

#### Patient Details

Twenty patients with coronary CTO were enrolled consecutively from November 3, 2009, to January 5, 2011. Baseline characteristics are shown in Table 1. All patients were male; the median age was 63 years (range, 43–79 years); and 35% were diabetic. A previous myocardial infarction was known in 25% of cases, and left ventricular ejection fraction was 55 ± 10%. Three patients (15%) had Q waves on their ECG in the territory of the CTO artery; 1 patient had viability on magnetic resonance imaging, and the other 2 patients had hypokinesia in the CTO territory by echocardiography. Two patients had a previous coronary artery bypass graft surgery. By history, the median occlusion age was 12.5 months (Q1 = 10.5 months, Q3 = 48 months). The median time since the initial first documentation of the occlusion on coronary angiography was 6 months (Q1 = 4.5 months, Q3 = 12.5 months), with a range of 1 to 60 months. The CTO was located in the left anterior descending artery in 45%, the left circumflex artery in 30%, and the right coronary artery in 25% of the cases (Table 2). The median occlusion length was 18 mm (Q1 = 15 mm, Q3 = 25 mm), and one third of the lesions were $>20$ mm long. Blunt entry was present in 55% of the cases.

#### Details of Previously Failed Attempts

The mean number of guide wires used per case in the initial failed attempt was 3.4 ± 0.9 (range, 2–5). Guide wire characteristics were grouped into 3 categories: (1) polymer-jacketed–tip guide wires (eg, Pilot, Whisper, Fielder XT); (2) exposed-coil, moderate-stiffness guide wires (eg, Cross-it XT 100 and 200, Vascular Progress 40 and 80, Miracle Bros 3, 4.5, and 6); and (3) exposed-coil, stiff-tip guide wires (eg, Progress 120T and 200T, Miracle Bros 12, Confianza Pro 9 and 12). A guide wire from each of the 3 categories was used

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD), y</td>
<td>63 ± 11</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Family history CAD, n (%)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Former/current smoker, n (%)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>CCS angina class II/III, n (%)</td>
<td>10/9 (50/45)</td>
</tr>
<tr>
<td>LVEF (mean ± SD), %</td>
<td>55 ± 10</td>
</tr>
<tr>
<td>Q waves in the CTO territory, n (%)</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass graft surgery; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; LVEF, left ventricular ejection fraction; and CTO, chronic total occlusion.
in 9 patients (45% of the study patients) and from 2 categories in an additional 10 patients (50%). A guide wire from only 1 category (category 2) was used in 1 patient. The mean fluoroscopy time per failed case was 38 ± 19 minutes. Fluoroscopy time exceeded 20 minutes in 90% and 30 minutes in 60%. The mean contrast use per case was 288 ± 134 mL and exceeded 200 mL in 70% of cases.

Clinical Outcome and AEs

Collagenase was safely delivered to all 20 patients at the 4 dosing levels, ranging from 300 µg to 1200 µg. The intra-coronary injection of collagenase was well tolerated without angiographic dissections or abnormalities in cardiac enzymes, ECG changes, or echocardiographic changes. The median fluoroscopy time and contrast use for the collagenase delivery procedure were 14.1 minutes (Q1=11 minutes, Q3=19 minutes) and 165 mL (Q1=120 mL, Q3=205 mL), respectively.

In all cases, the PCI attempt was made 18 to 24 hours after the collagenase dose with no safety signals coming from any safety parameter evaluated. There were 5 AEs in the study, including 3 non–ST-segment–segment elevation infarctions, 1 asymptomatic small pericardial effusion, and 1 case of lung metastases in a patient with previously undiagnosed colon cancer, which was an incidental finding on the 3-month CT coronary angiogram. Three patients (15%), 1 each in the 300-, 600-, 900-µg dose cohorts, had creatine phosphokinase elevations after PCI (total creatine kinase, 411, 493, and 330 IU/L; creatine kinase-MB mass, 16, 54, and 80 ng/mL), all due to side-branch occlusions at the proximal end of the occlusions. These non–ST-segment–elevation infarctions had uncomplicated hospital courses. Serial echocardiographic studies identified only a small (<1 cm), asymptomatic pericardial effusion in 1 patient in the third dose cohort (900 µg) at 1 day after the PCI attempt.

No deaths or unexpected SAEs were reported during the study. There were 3 SAES, which included the 3 non–ST-segment–elevation infarctions because the event prolonged hospitalization (by 1 day in 2 patients and 2 days in 1 patient). The SAEs were deemed not to be related to the study drug as judged by the DSMB but rather were expected as a result of the procedure. There did not appear to be any dose relation-

Table 2. Lesion Characteristics

<table>
<thead>
<tr>
<th>LAD/LCx/RCA, %</th>
<th>45/30/25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median occlusion age by history (Q1, Q3), mo</td>
<td>12.5 (10.5, 48)</td>
</tr>
<tr>
<td>0–3 mo</td>
<td>1</td>
</tr>
<tr>
<td>4–6 mo</td>
<td>2</td>
</tr>
<tr>
<td>7–12 mo</td>
<td>7</td>
</tr>
<tr>
<td>1–2 y</td>
<td>4</td>
</tr>
<tr>
<td>&gt;2 y</td>
<td>6</td>
</tr>
<tr>
<td>Median lesion length (Q1, Q3), mm</td>
<td>18 (15, 25)</td>
</tr>
<tr>
<td>Lesion length &gt;20 mm, %</td>
<td>35</td>
</tr>
<tr>
<td>Median reference diameter (Q1, Q3), mm</td>
<td>2.93 (2.35, 3.26)</td>
</tr>
<tr>
<td>Blunt entry, %</td>
<td>55</td>
</tr>
<tr>
<td>Side branch at occlusion, %</td>
<td>45</td>
</tr>
</tbody>
</table>

| Median fluoroscopy time wire crossing (Q1, Q3), min | 20.6 (14.0, 43.7) |
| Total case (Q1, Q3), min | 59.5 (42.7, 63.0) |
| Stent (average±SD), n | 2.6±0.9 |
| Stent length, mm | 66.2±25.6 |
| Stent diameter, mm | 2.95±0.35 |

Table 3. Percutaneous Coronary Intervention Procedural Data

| Successful guidewire crossing, n (%) | 15 (75) |
| Median contrast volume (Q1, Q3), mL | 438 (328, 542) |
| Median fluoroscopy time wire crossing (Q1, Q3), min | 20.6 (14.0, 43.7) |
| Total case (Q1, Q3), min | 59.5 (42.7, 63.0) |
| Stent (average±SD), n | 2.6±0.9 |
| Stent length, mm | 66.2±25.6 |
| Stent diameter, mm | 2.95±0.35 |

Q1 indicates 25th percentile; Q3, 75th percentile.

ship with respect to AEs or severity of the events, with the highest-dose cohort (1200 µg) having no reported cardiovascular events in any of the 5 patients included.

All patients underwent percutaneous revascularization on day 1, and guide wire crossing was successful in 15 cases (75%) with Thrombolysis in Myocardial Infarction grade 3 flow (Table 3). Stenting was done successfully in 14 cases on day 1. In 1 case of a circumflex occlusion, the guide wire was successfully directed into a smaller obtuse marginal branch rather than the desired obtuse marginal branch. This patient was brought back 1 month later and a stent was placed in the smaller obtuse marginal branch because the guidewire still only entered this branch. In 1 case of a left anterior descending artery CTO, the initial guide wire crossing was mistaken due to side-branch occlusions at the true distal lumen. The occlusion was easily crossed (fluoroscopy crossing time <5 minutes) and stented when the patient was brought back at 3 months for a reattempt. Thus, the overall stenting success rate in the study was 80%.

CTO crossing was unsuccessful in 4 cases. One case was a left anterior descending artery occlusion in which the OTW balloon catheter could not be adequately advanced up to the CTO, and the infusate was injected into a side branch. This prompted the change to a fine-cross microcatheter for injection of collagenase. The other 3 cases were in right coronary artery occlusions: 2 were due to calcification (heavy in 1 case and a very localized but linear calcification in the other case) and 1 was in a very long (35-mm length), tortuous CTO.

In 75% of the successfully crossed occlusions, soft poly-jacketed–tip guide wires (Whisper, Pilot-50, and/or Fielder XT) either completely crossed the lesion (8 cases) or were advanced to the very distal end of the CTO and required a stiff-tip guide wire (Confianza Pro 9 or Pro 12) to reenter a short distance into the ongoing lumen (4 cases). In 25% of the cases, a stiff-tip guide wire was the principal guide wire used for the CTO crossing.

The mean number and length of stents were 2.6±0.9 and 66.2±25.6 mm, respectively. The median fluoroscopy guide wire crossing time was 20.6 minutes (Q1=14 minutes, Q3=43.7 minutes). The median total fluoroscopy time for the entire case was 59.5 minutes (Q1=42.7 minutes, Q3=63.0 minutes), and the median contrast use was 438 mL (Q1=328 mL, Q3=542 mL).

CT coronary angiograms were performed in 19 patients at 3 months. All stented arteries remained patent, and there was
no evidence of aneurysm or dissection in any arteries. No myocardial or pericardial effects were evident. One patient who could not undergo CT angiography because of fast heart rate and contraindication to β-blockade underwent repeat angiogram at 6 months, which showed patent coronary stents. Two patients had repeat revascularization within 6 months owing to asymptomatic restenoses on coronary CT angiograms: proximal to the stents in 1 patient and distal to the stents in 1 patient.

Clinical improvement was evident in the overall patient population, with a reduction from baseline CCS angina class 2.5±0.6 to 0.9±0.9 at 3 months (P<0.001).

Discussion

The presence of a CTO remains the most common reason for referral to bypass surgery. In the Bypass Angioplasty Revascularization Investigation (BARI) trial, the presence of chronic occlusion was the main reason that patients were deemed unsuitable for percutaneous transluminal coronary angioplasty and was present in 68% of the 8000 patients.17

The same preponderance was noted in the recently published Syntax registry,18 in which the surgical arm had a significantly higher prevalence of chronic occlusions compared with the percutaneous revascularization arm, 56.4% versus 36.5%, respectively.

The principal finding of the phase 1, dose-escalation CTO-1 clinical study is that collagenase delivery into chronic occlusions is feasible and safe and is associated with encouraging guide wire crossing success rates in symptomatic patients with previously failed attempts. The rationale of using collagenase in CTO is based on evidence from human pathology and experimental model studies indicating that collagen is the major component of the occlusions, particularly at the proximal fibrous cap.7–9 Collagenase has recently been shown to successfully treat Dupuytren contracture, another disease characterized by excessive collagen accumulation.19 Extensive preclinical studies in a rabbit femoral artery chronic occlusion model have previously shown that local delivery of collagenase significantly improved guide wire crossing.10,11

It is generally acknowledged that success rates are lower in reattempt CTO cases than in first attempts. In the Japanese CTO (J-CTO) registry, reattempts were reported in 54 cases (10.2% of the overall study cases).20 The success rate for guide wire crossing was 72.2% and was significantly lower than first attempt cases. The actual lesion success rate (final diameter stenosis <50%) was 68.5%. In the European CTO (ERCTO) registry, Galassi et al.21 reported a 76.1% success rate on reattempts of 498 CTO lesions. These success rates in previously attempted CTO were achieved through innovations in technology and technique, including the retrograde approach. In the J-CTO registry, the retrograde approach was used in 25% of the overall cases, although specific data on reattempts are not available. In the ERCTO registry, the overall registry had 11.8% cases attempted by retrograde approach; however, the retrograde approach was used in 24% of the reattempt cases (Dr A. Galassi, personal communication). Although the retrograde approach has been shown in 1 study to improve CTO success rates significantly in complex cases22 (58.9% versus 75.2%), this particular technique is currently limited to a small number of highly trained, experienced operators because it more complex than the antegrade approach and uses increased radiation dose and contrast use. The case selection between these 2 registries and our study cannot be reliably compared. However, the ability to cross complex CTO lesions successfully in an antegrade approach, particularly with soft-tip guide wires, should be particularly appealing to interventional operators provided that larger, prospective trials show similar results.

The CTO-1 study patients had many highly complex lesion characteristics. By protocol design, all patients had 1 failed angioplasty attempt, and 1 patient had undergone 2 unsuccessful attempts. The details of the failed initial PCI attempt are consistent with a significant effort in almost all of the cases. Occlusion length (median, 18 mm; one third of the lesions were >20 mm) and the high percentage of lesions with blunt entry (55%) and bridge collaterals (30%) also are markers for procedural difficulty. Despite these adverse features, the overall guide wire success rate in our study population was 75%. Moreover, guide wire crossing was accomplished with soft-tip guide wires (tip loads, 1.0–1.5 g) through the entire occlusion or up to the distal cap in 75% of the cases, consistent with significant softening of the hard, occlusive plaque with the collagenase. Even in cases when stiffer-tip guide wires were required for traversing most of the CTO distance, the collagenase likely had an effect, considering the previous failure in these lesions with any type of guide wire and/or technique. Recent data in preclinical models have shown a significant reduction of puncture forces in the proximal cap of CTO in collagenase-treated arteries (unpublished data). The requirement of stiffer-tip guide wires to cross the most distal part of the occlusion in some cases in this study suggests that the effect of the collagenase is predominantly at the proximal fibrous cap and the body of the CTO, with lesser effects at the distal cap.

The technique of collagenase injection into the occlusion is a critical aspect of this procedure. On the basis of our experience in preclinical studies, the initial patients were injected through an OTW balloon catheter positioned either into the first part of the occlusion or just proximal to the lesion. Because of limitations in catheter flexibility in negotiating bends in the coronary artery anatomy before the occlusion, it was difficult in several cases to advance the OTW balloon as distally as desired, even when the guide wire was advanced into the first part of the occlusion. In 1 case (case 6), the collagenase was injected despite suboptimal OTW position, and it was evident that the infusate was diverted down a side branch. This was the only case in which a guide wire could not be advanced any distance at all into the occlusion on the next day. As a result of this technical limitation, we changed to the fine-cross microwire that could be advanced in all cases into the first part of the CTO regardless of the coronary anatomy. Although not encountered in this study, failure to advance the microwire properly into the initial part the occlusion should be considered a contraindication to collagenase use to avoid loss of the collagenase infusate into a side branch.
The microcatheter was routinely advanced ∼2 to 3 mm into the occlusion to ensure that the injection would be inside the occlusion. The collagenase was injected slowly, essentially drop by drop, over 15 minutes to ensure no damage inside the CTO; the final angiogram in all cases confirmed the absence of any dissections or contrast retention after the collagenase injection. In some cases, there was tactile sensation of some resistance to the injection, but it could always be accomplished with gentle pressure on the injection syringe. The initial angiogram performed the next day did not appear substantially different from the post–collagenase injection angiogram, and no dissections were evident. However, the fine-cross catheter very easily advanced deeper into the CTO in many of the cases on the next day, consistent with overnight plaque-softening effects of the collagenase.

In the 4 failed cases, there was a significant contributing reason. The failed cases highlight the essential requirement for proper collagenase injection and for appropriate lesion selection; the main reasons for failure were excessive calcification, lesion length, and tortuosity of the occluded segment. From this initial experience, we recommend against using collagenase in heavily calcified vessels (collagenase does not act on calcium) and lesions >30 mm in length.

Percutaneous revascularization of chronic occlusions, even with collagenase, remains a complex procedure. The CTO arteries in our study were diffusely diseased before and after the occlusion, requiring treatment by a mean stent length of >60 mm. Previous CTO studies have similarly reported long mean stents in the range of 45 to 56 mm.20–23 The overall fluoroscopy times (guide wire crossing and total procedure) and contrast use in this initial experience are still much longer than angioplasty procedures in nonoccluded arteries. There are also the additional fluoroscopy time and contrast use associated with the collagenase delivery procedure. Nevertheless, the success rate in revascularizing this challenging group of symptomatic, previously failed cases is very promising, and additional clinical experience with collagenase should improve procedure and fluoroscopy times and contrast use.

Future studies are required to demonstrate the safety and efficacy in larger patient populations. Several issues could be addressed in future studies. The maximum dose used in this study was based on preclinical toxicity studies and was tolerated without significant side effects. It is unclear whether the use of higher collagenase doses for more recalcitrant occlusions is necessary or tolerated. Our initial experience suggests that the dose of 1200 μg seems to be very reasonable in terms of safety and efficacy. Specific delivery devices to optimize the depth of penetration of the collagenase into the CTO may be desirable. Some technical challenges remain, especially crossing the distal part of the lesion where the softening effect of the collagenase was less evident. It is also possible that the collagenase could be combined with other crossing devices or techniques (eg, retrograde) to improve crossing rates and to shorten procedural times. The present treatment regimen requires a 2-day procedure. Previous preclinical work has shown that a 72-hour waiting period between delivery and guide wire crossing is also effective and, in some cases, may be more clinically convenient.10 Whether the collagenase procedure can be shortened into a single-day procedure remains to be determined; however, the time required for collagenase injection seems well suited to chronic occlusions diagnosed at the time of angiography when operators may have limited time to attempt the CTO given the prescheduled list of cases. The patient can then be brought back for revascularization at a more suitable time.

Conclusion

The CTO-1 clinical trial has shown that local delivery of collagenase into coronary CTO is feasible and safe, with encouraging guide wire crossing results in previously failed cases. Larger clinical trials are required to determine efficacy.

Acknowledgments

We would like to gratefully acknowledge the efforts and advice of the members of the DSMB, Dr Merrill Knudtson (chair), Dr Madhu Natarajan, and Dr Vitalijrazvijk, as well as Lyn Balleza and Elaine Hsu, the study coordinators.

Sources of Funding

This study was supported by the Canadian Institute of Health Research (grant MOP 93814).

Disclosures

Dr Strauss holds intellectual property on the use of collagenase in CTOs and is founder of Matrizyme Pharma Inc, a company that is commercializing collagenase for use in CTOs. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Chronic total occlusions (CTO) are common and have been identified in ≈20% to 30% of all coronary angiograms. The majority of patients are treated medically, with <10% of patients undergoing revascularization by percutaneous coronary interventions. The reluctance to attempt percutaneous coronary intervention in symptomatic patients is due in part to a lower success rate (≈70%–85%, depending on operator expertise and case selection) and prolonged procedure times. The Collagenase Total Occlusion-1 (CTO-1) trial is the first human coronary CTO experience of injecting collagenase into CTO, followed by a percutaneous coronary intervention attempt the next day. The study is based on extensive preclinical work showing that locally injected collagenase produced by Clostridium histolyticum directly into experimental CTO softens the collagen within the occlusive plaque and facilitates guide wire crossing. In the phase I, dose-escalation CTO-1 Trial, increasing doses of collagenase were successfully injected into CTO with a microcatheter. The main finding of the CTO-1 Trial is that collagenase delivery is feasible and safe, with no untoward clinical effects related to collagenase or the delivery technique. In this first-in-humans experience, the 75% success rate for guide wire crossing after collagenase treatment in 20 previously failed cases was encouraging, particularly because crossings were achieved with soft-tip guide wires in 75% of the successful cases. The CTO-1 Trial offers an innovative, biologically based approach that may improve percutaneous coronary intervention results in difficult-to-treat coronary chronic occlusions. Future studies are needed to determine the utility of this new therapeutic approach.
Collagenase Total Occlusion-1 (CTO-1) Trial: A Phase I, Dose-Escalation, Safety Study
Bradley H. Strauss, Azriel B. Osherov, Sam Radhakrishnan, G.B. John Mancini, Allison
Manners, John D. Sparkes and Robert J. Chisholm

Circulation. 2012;125:522-528; originally published online December 16, 2011;
doi: 10.1161/CIRCULATIONAHA.111.063198
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/125/3/522

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located,
click Request Permissions in the middle column of the Web page under Services. Further information about
this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/