BlueCross BlueShield of Kansas City

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Injectable Clostridial Collagenase for Fibroproliferative Disorders

Policy Number: 5.01.19
Origination: 01/2011
Last Review: 12/2013
Next Review: 12/2014

Policy

BCBSKC will provide coverage for injectable clostridial collagenase when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Injectable clostridial collagenase for the treatment of Dupuytren's contracture in adult patients with a palpable cord may be considered **medically necessary,** for up to three injections at intervals of at least thirty days.

When Policy Topic is not covered

Injectable clostridial collagenase is considered **investigational** for all other indications including, but not limited to, Peyronie's disease, and adhesive capsulitis.

Considerations

This Blue Cross and Blue Shield of Kansas City policy statement is consistent with the Blue Cross and Blue Shield Association Policy 5.01.19

Description of Procedure or Service

Collagenases are enzymes that digest native collagen and are being evaluated for treatment of fibroproliferative disorders such as Dupuytren's contracture and Peyronie's disease. Clostridial collagenase is a bacterial collagenase derived from *Clostridium histolyticum*. Treatment of Dupuytren's contracture consists of injection of collagenase into the cord followed by manipulation of the finger if contracture persists. Injection may be done up to 3 times at 4-week intervals.

Injection with clostridial collagenase is intended to provide a nonoperative treatment option for fibroproliferative disorders. Fibrotic tissue disorders, characterized by excessive collagen deposits, can affect the musculoskeletal system, causing pain and limitation of movement and reduction of joint range of motion. Dupuytren's disease and adhesive capsulitis are such musculoskeletal disorders; Peyronie's disease is another example.

The mechanisms that contribute to the pathology are poorly understood. In Dupuytren's disease, collagen deposition results in nodules and cords in the palm and fingers resulting in pitting of the overlying cutis and flexion contractures. The standard of care for Dupuytren's disease is surgery, most commonly open fasciectomy. Other surgical procedures are percutaneous fasciotomy and needle fasciotomy. Surgery is recommended in patients with functional impairment and metacarpophalangeal (MCP)-joint contractures of 30 degrees or more. There is no effective pharmacotherapy. Adhesive capsulitis or "frozen shoulder" is treated with physiotherapy and mobilization in combination with analgesics or nonsteroidal anti-inflammatory drugs. Corticosteroid injection is used with caution. The prevalence of Dupuytren's disease and adhesive capsulitis is estimated at 3–6% and 2–3%, respectively, in the general population and increases with advancing age. Both conditions are more common in patients with diabetes or thyroid disease. Dupuytren's disease is more common in men, and adhesive capsulitis more common in women. (1)

Peyronie's disease is the development of abnormal scar tissue, or plaques, in the tunica albuginea layer of the penis causing distortion, curvature, and pain usually during erection. It occurs in 3–9% of men, most commonly between the ages of 45 and 60. In some cases, plaque does not cause severe pain or curvature, and the condition resolves on its own. In severe cases, erectile dysfunction can occur. The goal of treatment is to reduce pain and maintain sexual function. Treatments in early stages (before calcification) include vitamin E or para-aminobenzoate tablets (e.g., Potaba) although studies of oral therapies demonstrate inconsistent benefit. Intralesional injection therapy consisting of injection of interferon-alpha-2b or calcium channel-blockers (e.g., verapamil) is the current standard of therapy. (2) Surgical procedures involve the excision (removal) of hardened tissue and skin graft, the removal or pinching (plication) of tissue opposite the plaque to reduce curvature (called the Nesbit procedure), a penile implant, or a combination of these.

Regulatory Status

In February 2010, the U.S. Food and Drug Administration (FDA) approved Auxilium Pharmaceutical Inc.'s biologics license application for clostridial collagenase histolyticum (Xiaflex) for treatment of adult patients with Dupuytren's contracture with a palpable cord. The FDA labeling for Xiaflex states that up to 3 injections at 4-week intervals may be given into a palpable Dupuytren's cord with a contracture of a metacarpophalangeal (MCP) joint or a proximal interphalangeal (PIP) joint.

Rationale

This policy was originally created in 2010 and was regularly updated with searches of the MEDLINE database. The most recent literature search was performed for the period January 2011 through August 2011. Following is a summary of the key findings to date.

A number of nonsurgical interventions for fibroproliferative disease have been studied. Investigations of a potential role for injectable clostridial collagenase have been ongoing over a period of 20 years. FDA approval was granted in 2010 for treatment of Dupuytren's contracture with a palpable cord. Some authors include collagenase among standard injection therapies for Peyronie's disease. Use of the material for treatment of conditions other than Dupuytren's is an off-label application.

Dupuytren's Disease (Dupuytren's Contracture)

Chen and colleagues published a systematic review in 2011 of various treatments for Dupuytren's contracture. (3) Studies published through December 2010 were examined and included 4 prospective studies (including 2 randomized studies) on collagenase injections, 6 studies on open partial fasciotomy (including 2 randomized studies) and 3 studies on needle aponeurotomy. Sample sizes for all of the studies included in the review ranged from 13–261 patients. The authors found recurrence rates for collagenase injections (mean follow-up times of 120 days to 4 years) ranged from 10–31%. Needle aponeurotomy had the highest recurrence rates of 50-58% (mean follow-up of 3-5 years) which were significantly higher than the open partial fasciectomy recurrence rates of 12–39% (mean follow-up time of 1.5–7.3 years). Additionally, open partial fasciectomy recurrence rates were significantly higher than collagenase injection. Complications occurred most often with open partial fasciectomy although 2 cord ruptures were reported with collagenase injection. The authors concluded further studies are needed to understand the long–term outcomes of these interventions and how to address contracture recurrence. It is also noted it is unclear whether collagenase injection can be used for Dupuytren's revision.

In 2009, Hurst and colleagues published results from CORD I, a randomized, double-blind placebo-controlled, multicenter trial (16 sites) of collagenase clostridium histolyticum for Dupuytren's contracture with 308 subjects with joint contractures of 20 degrees or more. (4) This study was included in the Chen review described above. (3) Joints were stratified according to type (metacarpophalangeal [MCP] joints or proximal interphalangeal joint [PIP]) and severity of contracture and randomly assigned in a 2:1 ratio to receive up to 3 injections of either collagenase or placebo in the contracted collagen cord at 30-day intervals. Secondary and tertiary joints were identified for possible subsequent injections. Joints were manipulated one day after injection if necessary. The primary endpoint was reduction in contracture to 0–5 degrees of full extension 30 days after last injection. Twenty-six secondary endpoints were also evaluated. Recurrence of contracture was defined as an increase in

joint contracture equal to or greater than 20 degrees and was considered an adverse event. Efficacy results were based on 306 primary joints: 203 injected with collagenase and 103 injected with placebo. In the collagenase-treated group, 130 of 203 (64%) cords met the primary endpoint versus 7 of 103 (6.8%) placebo-injected cords ($p<0.001$). More than half of the collagenase-injected joints that did not meet the primary endpoint did not receive the maximum allowable number of injections, most commonly because a cord could not be palpated or the patient was satisfied with the result. Median time to reach the primary endpoint for collagenase-treated joints was 56 days. At the 90-day visit, there was no recurrence of contracture in collagenase-treated primary joints that had reached the primary endpoint.

When analyzed by joint type, more collagenase-treated joints achieved the primary endpoint than placebo (MCP 76.7% vs. 7.2% and proximal PIP joint 40.9% vs. 5.9%, both respectively) ($p<0.001$ for both comparisons). The mean change in contracture from baseline to 30 days after last injection was 48.0 to 7.2 degrees in the collagen-injected MCP joints and 45.4 to 43.1 degrees in the placebo-injected MCP joints. Thirty days after last injection 84.7% of collagenase-injected joints versus 11.7% of placebo-injected joints showed clinical improvement. Results were better in MCP joints than in PIP joints: 94.0% versus 67.1%, respectively, in the collagenase group and 11.6% versus 11.8%, respectively, in the placebo group. Overall, 96.6% of patients who received collagenase reported at least one treatment-related adverse event. They had significantly more injection- and manipulation-related events, such as contusion, hemorrhage, injection-site pain, upper extremity pain, and lymphadenopathy ($p\leq0.02$), than patients who received placebo injection. Most were mild or moderate in intensity; however 20 patients in the collagenase group and 2 in the placebo group reported events that were severe in intensity. Three severe adverse events were considered to be treatment related: a case of complex regional pain syndrome and 2 tendon ruptures, both requiring surgical procedures. The authors note that the timeframe of this study was insufficient to assess recurrence, and they could not make any claims about this outcome.

In a letter to the editor in response to publication of the study, Holzer and Holzer comment that successful treatment of Dupuytren's disease correlates with the percentage of excised Dupuytren's tissue and the extent of the intervention. (5) They caution that the value of collagenase injection must be confirmed in a long-term follow-up study that focuses on the recurrence rate.

In 2010, Gilpin and colleagues published results of the CORD II study. (6) In this study, 66 patients were randomized to receive collagenase injection (45 cords) or placebo (21 cords) in the 90-day, double-blind phase followed by an open label phase of 9 months. The authors reported, within 30 days, collagenase injections resulted in significantly more cord contracture improvement from baseline to within 0-5 degrees of normal than placebo (44.4% vs. 4.8%). Results after the open-label treatment were reported to be similar to the double-blind phase. Recurrence of contracture (defined as increase of contracture to 20 degrees or more) did not occur during the 12-month follow-up. All study participants experienced mild adverse events (e.g., swelling and pain at injection site). Three serious adverse effects related to the treatment were reported. A flexion pulley rupture of the left small finger occurred in one patient while rapid thickening of the treated cord and sensory abnormalities occurred in another patient.

Watt and colleagues, in 2010, reported on a Phase II clinical trial of 23 patients of which 8 patients completed 8-year follow-up. (7) In the isolated MCP group (n=6), average contracture was 57 degrees before treatment, 9 degrees at 1 week, 11 degrees at 1 year, and 23 degrees at 8-year follow-up. Four of 6 patients experienced recurrence by the 8 year follow-up. In the isolated PIP joint group (n=2), both patients had recurrence by 8-year follow-up. Outcomes at specific intervals between 1 year and 8 years were not reported. Potential bias in patient selection and the small number of patients precludes drawing conclusions from this report.

In a 2010 review, Desai and Hentz make several observations regarding the role of collagenase in the treatment for Dupuytren's contracture. (8) They recommend caution when treating the small finger; all three tendon ruptures seen across all studies reported to the FDA and adverse events of boutonniere deformity and pulley injury occurred in the small finger. An active immune-response was seen in patients after injection of collagen in the clinical trials, which suggests the possibility that effectiveness of subsequent injections might be impacted. The authors also note that long-term effects of repeat injections and contracture recurrence have yet to be studied, and direct comparisons with the current gold standard, palmar fasciectomy, have not been made.

In 2007, Badalamente and Hurst reported on patients who participated in a double-blind Phase III RCT comparing collagenase and placebo injections. (9) During the double-blind and open-label phases, 62 joints (31 MCP and 31 PIP) were treated in 35 patients. Fifty-four (87%) were clinical successes. Twenty-seven joints were followed up for 24 months. Over the 24 months following the last injection, 5 joints had recurrences (1 MCP and 4 PIP), 1 before 12 months, 2 at 12 months, and 2 at 24 months after treatment. Three of these patients subsequently underwent fasciectomy. The most common adverse events were local reactions to injections. The limited patient follow-up makes it difficult to reach conclusions from this study.

Peyronie's Disease

Authors of a 2007 systematic review of plaque injection therapy included 2 studies of collagenase in their analysis. (10) Both papers reported positive treatment outcomes. One study was rated, according to the Oxford Centre for Evidence-Based Medicine criteria, as level 2 (randomized controlled trial [RCT] with low power or <80% follow-up/retention or good-quality, randomized prospective cohort study) and the other level 4 (case series or poor-quality cohort or case-control study). These 2 studies are noted below. (11 , 12) Agents used in the other 19 studies reviewed were corticosteroid, verapamil, and interferon. In a 1985 paper on a series of 31 men treated, 20 showed improvement. (11) Pain was eliminated in 13 of 14 patients who experienced pain before treatment. One small corporeal rupture at the injection site was reported in one patient. No significant adverse events were reported in 9.8 months of follow-up. In a 1993 randomized, placebo-controlled, double-blind study with 49 subjects reported by the same author, the effects of collagenase and placebo on plaque size and penile deformity were investigated. For the group as a whole, treatment with collagenase was significantly more effective ($p<0.007$). Patients with lesser deformity responded more favorably to treatment. (12) In 2008, Jordan reported on a series of 25 patients with well-defined plaque treated with 3 intralesional injections of clostridial collagenase over 7–10 days with repeat treatment at 3 months. (13) Primary endpoints were changes from baseline in deviation angle and plaque size. Significant decreases from baseline were achieved in the mean deviation angle at months 3 ($p=0.0001$) and 6 ($p=0.0012$), plaque width at months 3 ($p=0.0052$), 6 ($p=0.0239$), and 9 ($p=0.0484$), and plaque length at months 3 ($p=0.0018$) and 6 ($p=0.0483$). More than 50% of patients in this series considered themselves "very much improved" or "much improved" at all time points in the study, and the drug was generally well-tolerated.

Adhesive Capsulitis

No studies including patients with adhesive capsulitis were identified in the literature search.

Ongoing Clinical Trials

Several studies were identified on injectable clostridial collagenase injections in a search of the National Institutes of Health clinical trials database at clinicaltrials.gov, including industry-sponsored studies of collagenase injections for Dupuytren's contracture. In the CORDLESS observational study (Collagenase Optimal Reduction of Dupuytren's - Long-term Evaluation of Success Study), the long-term durability and safety of clostridial collagenase injections for Dupuytren's contracture will be evaluated yearly in 600 patients (NCT00954746). This trial began in July 2009, is currently enrolling by invitation only and is expected to be completed in March 2013. In a phase IV, randomized trial, the effects of delayed manipulation of digits following collagenase injections for the treatment of Dupuytren's contracture will be examined in 60 patients (NCT01226121). Collagenase injections to the thumb for Dupuytren's contracture treatment will be studied in 10 patients in NCT01265420. Outcomes

after collagenase injection for Dupuytren's contracture will be studied in a phase III study of 250 patients followed for 11 months (NCT01229436). This trial is expected to be completed in September 2010. The safety and efficacy of 2 injections of clostridial collagenase into the same hand of 60 patients with multiple Dupuytren's contractures will be evaluated in an open-label, phase III study. (NCT01407068).

Three phase III studies were identified to evaluate clostridial collagenase injections for patients with Peyronie's disease that are expected to be completed in March 2012 (NCT01243411, NCT01221623 and NCT01221597). No studies were identified on collagenase injections for adhesive capsulitis.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2010
In response to requests, input was received from 2 physician specialty societies and 6 academic medical centers while this policy was under review in 2010. The input was mixed, with half those providing input agreeing that use of this agent is investigational. While there was support for use in Dupuytren's contracture, comments were made about the limited amount of data on long-term outcomes and durability.

2011
In response to requests, input was received from 2 physician specialty societies (2 reviews) and 5 academic medical centers (6 reviews) while this policy was under review in 2011. Two reviewers indicated injectable clostridium collagenase is investigational for the treatment of Dupuytren's contracture noting lack of long-term data and head-to-head trials comparing collagenase to surgical options. However, despite considering this treatment investigational due to insufficient long-term evidence of effectiveness, 1 reviewer noted injectable clostridial collagenase for Dupuytren's contracture is FDA approved and there is evidence of short-to-medium term effectiveness available. Five reviewers indicated injectable clostridial collagenase for Dupuytren's contracture may be considered medically necessary. These reviewers noted this is a treatment alternative to surgery. This was considered to be near-uniform support for the medical necessity of injectable clostridial collagenase for the treatment of Dupuytren's contracture.

Four reviewers agreed injectable clostridium collagenase is investigational for the treatment of Peyronie's Disease. One of these reviewers also commented that while this treatment is considered investigational, it may be indicated for Peyronie's disease when it is bothersome noting surgery is intrusive. Four reviewers also agreed injectable clostridium collagenase is investigational for the treatment of adhesive capsulitis. Finally, 6 reviewers agreed injectable clostridium collagenase is investigational for all other indications.

Summary
In summary, the evidence from clinical trials suggests that injectable clostridial collagenase provides short-term release of contracture in Dupuytren's disease. While evidence of long-term recurrence rates is limited, this may be an appropriate treatment option in adult patients with a palpable cord based on short-term evidence of effectiveness and a preponderance of agreement from clinical input. Therefore, injectable clostridial collagenase may be considered medically necessary as an alternative to surgical options. A comparison of overall outcomes compared to surgical intervention may be useful; however, studies with direct comparisons are not available. Potentially serious adverse events also warrant further investigation. Small trials demonstrated short-term improvement in patients with Peyronie's disease. Larger trials directly comparing outcomes with current treatment options are required. Therefore, based on available evidence and clinical input, injection of this agent is considered investigational for all other treatment indications, including Peyronie's disease and adhesive capsulitis.

Practice Guidelines and Position Statements
Ralph and colleagues developed guidelines for the treatment of Peyronie's disease in 2010. (14) These guidelines indicate surgery is the treatment of choice although conservative management is an appropriate option.

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Billing Coding/Physician Documentation Information

J0775 Injection, collagenase clostridium histolyticum, 0.01 mg
20527 Injection, enzyme (eg, collagenase), palmar fascial cord (ie, Dupuytren's contracture)
26341 Manipulation, palmar fascial cord (ie, Dupuytren's cord), post enzyme injection (eg, collagenase), single cord

Additional Policy Key Words

Xiaflex

Related Topics

N/A

Policy Implementation/Update Information

2/2011 New Policy Titled Injectable Clostridial Collagenase for Fibroproliferative Disorders
12/2011 Policy updated with literature review; reference numbers 3, 6 and 14 added. Policy statement changed to may be considered medically necessary for Dupuytren's contracture in adult patients with a palpable cord. All other indications remain investigational.
12/2013 Policy updated with literature review through September 11, 2013; reference numbers 3, 9-10, 14, and 19 added; no change in policy statements.