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REVIEW

Chemonucleolysis for Lumbar Disc Herniation: History and Current State of the Technology

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Abstract: The most common cause of radicular leg pain is lumbar disc herniation (LDH). LDH occurs when the central disc material, predominantly the nucleus pulposus, is displaced beyond the margins of the disc, compressing the spinal nerve roots and in turn causing radicular leg pain. Patients with persistent LDH symptoms that do not respond to conservative management have limited treatment options other than surgery. There has been a resurgence of interest in chemonucleolysis, in which an enzyme or other substance is directly injected into the intervertebral disc with the goal of reducing the size of the nucleus pulposus, relieving pressure on the nerve roots. Chemonucleolysis with chymopapain was widely used in the 1980s and 1990s as an effective treatment for LDH that was less invasive than surgery. Following the discontinuation of chymopapain in 1999, no chemonucleolytic therapy has been commercially available in the US. SI-6603 (condoliase) is a mucopolysaccharidase that selectively degrades chondroitin sulfate glycosaminoglycan (GAG) chains in the nucleus pulposus. Condoliase is approved in Japan and recently demonstrated significant improvements in worst leg pain (vs sham) in a pivotal US phase 3 clinical trial. Chemonucleolytic agents with less substrate specificity include gelified ethanol and oxygen-ozone, which are under postmarket surveillance in Europe, as well as collagenase in China. The re-emergence of chemonucleolysis is anticipated to improve the treatment landscape for LDH, providing patients with the option to avoid more invasive surgical intervention.

Keywords: condoliase, SI-6603, intradiscal therapy, radicular leg pain, lumbar radiculopathy

Introduction

Lumbar disc herniation (LDH) is defined as the extrusion of the nucleus pulposus (and/or annulus fibrosus) beyond the normal margins of the intervertebral disc, compressing the spinal nerve roots. LDH occurs in an estimated 1% to 3% of the population and is the most common cause of radicular leg pain (ie, sciatica).[1,2] Specifically, the herniated material compresses the spinal nerve roots, which in turn produces pain that radiates to the leg and foot, with possible motor or sensory symptoms (ie, lumbar radiculopathy).[3,4] LDH most commonly occurs from age 30 to 50 years, the prime working years.[5,6] Patients with LDH experience substantial negative impacts on quality of life and productivity. Radiating leg pain is associated with increased pain, greater disability, poorer quality of life, more healthcare use, and more unemployment than those with nonspecific low back pain alone.[7,8]

The pathophysiology of LDH centers on the nucleus pulposus, which is comprised of random collagen fibers and radially arranged elastin fibers suspended in a gel containing aggrecan, the major proteoglycan of the nucleus pulposus.[9] Proteoglycans consist of a core protein and at least one glycosaminoglycan (GAG) chain attached to it.[10] Proteoglycans

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constitute approximately 15% of the nucleus pulposus, along with a small amount of collagen (4%), and water (80%). The GAG chains are primarily composed of keratin and chondroitin −4 and −6-sulfates, with chondroitin-6-sulfate being the most common, while the annulus fibrosus is composed of fibrocartilaginous material, mainly collagen.[11] When this outer annulus/posterior longitudinal ligament is intact, disc herniations are referred to as contained and further classified as protrusions or extrusions based on the shape of displaced disc material. Uncontained disc herniations lack an outer covering, and subclassifications include transligamentous extrusion or sequestration, in which there is discontinuity with the parent disc.[12]

First-line treatment for LDH-associated radicular leg pain is conservative management with pharmacologic approaches (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], gabapentin, opioids) and nonpharmacological treatments such as rest and physical therapy. LDH symptoms will resolve spontaneously or with conservative management in the vast majority (90%) of cases.[13,14] Epidural steroid injections (ESIs) provide short-term pain relief but negligible long-term benefits[15,16] and are not approved by the Food and Drug Administration (FDA).

Patients whose LDH symptoms do not respond to conservative therapy are often recommended for surgery. While discectomy is an effective procedure to decompress the spinal nerves and relieve LDH symptoms, the benefits of surgery on leg pain and disability have been shown to diminish over time.[17] In addition, surgery is associated with risks of intraoperative complications (eg, dural tear) and long-term consequences, such as pain recurrence, reherniation, and revision discectomy.[18–20] A follow-up to the Spine Patient Outcomes Research Trial (SPORT) and 2 meta-analysis have observed that prolonged LDH symptom duration (>6 months) is associated with worse pain and functional outcomes (ie, shorter duration, more positive outcomes) with or without surgery.[21–23] This reported adverse effect of longer symptom duration on outcomes suggests that timely treatment of persistent radicular pain may benefit patients with LDH.

Recently reviewed in detail elsewhere,[24] there is a substantial unmet clinical need for less invasive treatments that address the root cause of nerve compression and provide durable relief from LDH symptoms. While not currently commercially available in the US, chemonucleolysis has garnered great interest for its potential as a nonsurgical treatment option for patients with LDH. A 2007 Cochrane review estimated that chemonucleolysis could save approximately 70% of patients from requiring open surgery.[1] Various forms of chemonucleolysis were widely used to treat LDH in the 1980s and 1990s, offering a less invasive alternative to surgery, before being largely discontinued around 1999 despite physician and patient enthusiasm. Recently, chemonucleolysis has reemerged as a less invasive alternative to surgery being investigated to treat LDH-associated radicular pain. In this narrative review, we will (1) delve into the multifaceted history of chemonucleolysis, including the first chemonucleolytic agent chymopapain; (2) overview the development and clinical testing of a novel treatment, SI-6603 (condoliase), with recently published results of a positive US phase 3 pivotal clinical trial;[25] and (3) discuss additional chemonucleolytic therapies available in Europe and Asia, including gelified ethanol and collagenase, as well as chemonucleolytic agents in the clinical pipeline.

History of Chemonucleolysis with the Proteolytic Enzyme Chymopapain

Chymopapain was first isolated in 1941 from the uncrystallized latex derived from the fruit of the papaya tree (*Carica papaya*; Figure 1).[26] In 1964, Lyman Smith first described chemonucleolysis, which involves the direct injection of an enzyme or other substance into the intervertebral disc to degrade the nucleus pulposus. The enzyme chymopapain is nonspecific and exhibits a high level of proteolytic activity, through which it fragments proteoglycans in the nucleus pulposus, thereby decompressing the nerve.[27] After establishing the safety of chemonucleolysis with chymopapain in animal models, Smith published the first clinical report of intradiscal injections of chymopapain in patients with sciatica secondary to intervertebral disc herniations.[28] Following a sale of the patent for chymopapain, Baxter-Travenol formulated Discase, a product combining chymopapain B, cysteine sodium sulfite, and EDTA in lyophilized form.[26] Discase was tested clinically in approximately 2000 patients, with reports of ~70% success (ie, "return to work free of pain") in patients with LDH (N=668) who otherwise would have been indicated for surgery.[29] A study conducted at the Walter Reed Army Medical Center did not find a statistically significant difference between Discase and placebo, leading to controversy over the drug's efficacy; however, the Walter Reed study received criticism for lack of technical experience, insufficient drug dose, and lack of inert placebo.[26,30] In October 1975, Baxter-Travenol voluntarily withdrew its New Drug Application (NDA) for Discase, while investigational use continued in Canada and Great Britain.[11,26]

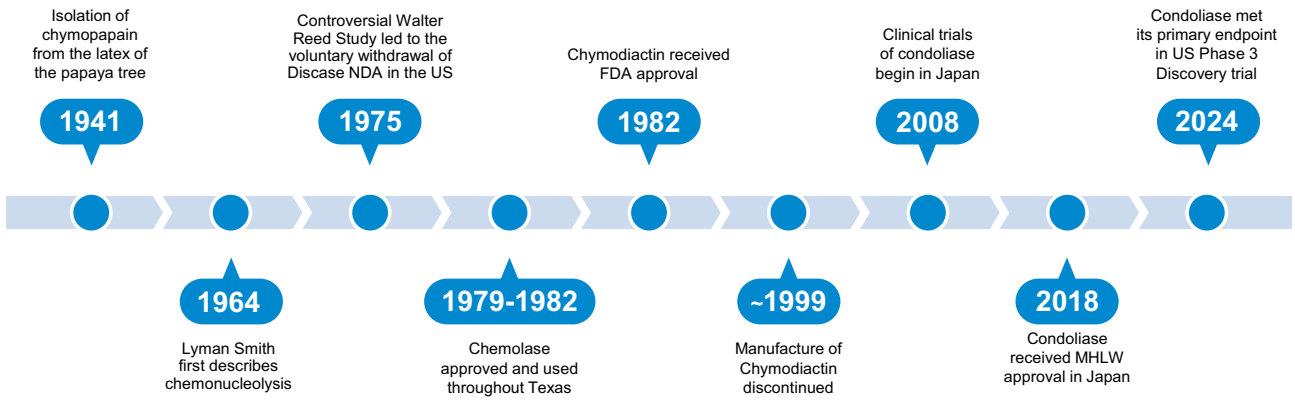

Figure 1 History of chemonucleolysis.
Abbreviations: FDA, Food and Drug Administration; MHLW, Ministry of Health, Labour, and Welfare; NDA, New Drug Application.

Although the drug was no longer commercially available in the US, physician enthusiasm for chemonucleolysis with chymopapain continued into the late 1970s. A coalition of physicians formed the Committee Advocating the Development and Use of Chymopapain to Eliminate Unnecessary Surgery (CADUCEUS) to reactivate the NDA and pursue national approval of chymopapain. CADUCEUS received state legislative approval from Texas, which had all the raw materials to produce chymopapain, but did not gain national approval. The new formulation Chemolase was used in Texas from 1980 to 1982.[26,30]

In 1979, Smith Laboratories introduced a purer chymopapain formulation under the name Chymodiactin.[30] Chymodiactin consisted of chymopapain along with sodium cysteinate hydrochloride, a stabilizer with properties of a reducing agent. Chymodiactin did not contain sodium bisulfite or edetic acid, which were removed from previous formulations to decrease the likelihood of adverse events and to increase drug stability. In a randomized controlled trial (RCT) in patients with LDH (N=108), Javid et al demonstrated that Chymodiactin was more efficacious than placebo, with a success rate of 82% (vs 41% placebo) 6 months after treatment administration. Back spasm was the most common adverse event, and no anaphylaxis was observed.[31] Chymodiactin received FDA approval in 1982.[30]

Chymopapain was widely used in North America, Europe, Australia, and Korea to treat LDH.[30,32,33] Subsequently, 3 randomized clinical trials demonstrated that chymopapain was superior to placebo in patients with LDH-associated radicular leg pain that did not respond to conservative therapy.[31,34,35] In a meta-analysis of 5 high-quality, randomized clinical trials (N=446 patients), chemonucleolysis with chymopapain was found to be more effective than placebo whether rated by the patient, surgeon, or an independent observer. Additionally, chymopapain reduced the likelihood of progressing to discectomy vs placebo.[1]

The potential for hypersensitivity and allergic reactions with chymopapain generated much controversy. The overall reported incidence of anaphylaxis was approximately 0.5% to 1%, with variability across studies.[11,30] The risk of allergic reaction could be mitigated with prior testing for allergic sensitivity to papain and/or preventative pretreatment with histamine-receptor antagonists.[30] Other frequently reported adverse reactions included back pain and back spasm after injection.[11] A recent meta-analysis including >10,000 patients treated with chymopapain (17 studies conducted from the late 1960s to 1980s) reported a rate of serious adverse events (SAEs) of 1.6% and a rate of anaphylaxis of 0.4%.[36]

Around 1999, Abbott Pharmaceuticals discontinued production of Chymodiactin, effectively withdrawing chymopapain from the market,[26] for reasons which were not entirely clear. A 2002 citizen petition was filed, and in response the FDA subsequently determined that Chymodiactin "was not withdrawn from sale for reasons of safety or effectiveness."[37] While several chemonucleolytic agents are approved in other countries, chemonucleolysis has been unavailable in the US for the last 25 years (since ~1999). Several physicians have decried the absence of chemonucleolysis with chymopapain as an "unacceptable situation" in which a safe and minimally invasive treatment for LDH with demonstrable benefit is "denied" to patients.[33] Despite physician and patient desire for a less invasive treatment than surgery, no chemonucleolytic drug is approved in the US, leaving a gap in the treatment armamentarium for LDH.

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SI-6603 (Condoliase): A Nonproteolytic Enzyme for LDH-Associated Radicular Leg Pain

Development and Proposed Mechanism of Action

Condoliase (chondroitin sulfate ABC endolyase) is a mucopolysaccharidase isolated and purified from the Gram-negative rod-shaped bacterium *Proteus vulgaris* and has been investigated as a research agent since 1968.[38–40] Condoliase has an approximate molecular weight of 110 kDa and is composed of 997 amino acid residues.[41] It differs from chymopapain formulations in its lack of protease activity. Condoliase specifically targets chondroitin sulfate, which is abundant in the nucleus pulposus as GAGs, the side chains of proteoglycans.[42,43] By specifically degrading chondroitin sulfate, condoliase is thought to reduce water retention in the nucleus pulposus, which in turn reduces intradiscal pressure and relieves nerve root compression.[41]

A biochemical analysis of substrate specificity to various polysaccharides confirmed that condoliase has the highest substrate specificity for chondroitin sulfate, particularly chondroitin-4 and −6 sulfate – the predominant components of GAGs in the nucleus pulposus.[38] Condoliase also showed high specificity for chondroitin sulfate D, chondroitin sulfate proteoglycan, dermatan sulfate, and chondroitin.[38] Notably, condoliase degraded hyaluronan at very low rates.[38,44] In addition, keratan sulfate, heparin, and heparan sulfate were not found to be substrates for condoliase.[38,40] Specifically, condoliase acts by cleaving the glycosidic bond between D-glucuronic acid (GlcA) and N-acetyl galactosamine (GalNAc) in the chondroitin sulfate molecule, yielding a chondroitin sulfate unsaturated disaccharide with a double bond between C4 and C5 of the GlcA residue at the non-reducing end.[43]

Preclinical studies of condoliase demonstrated a favorable pharmacokinetic (PK) profile. In animal studies, condoliase remained in the intervertebral disc and retained its enzyme activity following injection. Condoliase exhibited low systemic exposure and was rapidly eliminated upon entering systemic circulation.[41] Further supporting its proposed mechanism of action, condoliase was found to induce a dose-dependent decrease in intradiscal pressure in sheep.[45] In veterinary investigational practice, condoliase also improved symptoms in dogs with herniated disc.[46] Collectively, these preclinical findings support the anticipated therapeutic effect of condoliase to reduce intradiscal pressure, which thereby decreases nerve root compression and improves herniated disc symptoms.[41]

Japanese Clinical Trials and Approval in Japan

In Japan, 2 RCTs were conducted to evaluate the efficacy and safety of condoliase in patients (aged 20 to 70 years) with radicular leg pain associated with contained LDH (protrusion or subligamentous extrusion) with no improvement after ≥6 weeks of conservative therapy.[39,47] A phase 2/3 dose-finding study (NCT00634946) evaluated the PK, pharmacodynamics (PD), efficacy, and safety of a single injection of condoliase (1.25, 2.5, 5 U) vs placebo in 194 patients with radicular leg pain due to LDH. At Week 13, the condoliase 1.25-U and 5-U groups showed significantly greater improvements in worst leg pain (as measured on visual analogue scale [VAS]) and neurological symptoms on the straight leg raise (SLR) test vs placebo. In addition, worst back pain, disability as measured by the Oswestry Disability Index (ODI), and quality of life as measured by 36-Item Short Form Survey (SF-36) scores showed improvements in each condoliase group. Condoliase was associated with significant reductions in disc height and intervertebral disc volume compared with placebo in a dose-dependent manner. All condoliase dose groups showed a greater reduction in the volume of the herniated mass vs placebo. A dose-response relationship was also observed in the rate of adverse drug reactions and imaging changes. While condoliase was efficacious at all 3 doses tested, the dose-dependence of the incidence of adverse drug reactions (ADRs) and changes in imaging parameters led to the selection of 1.25 U as the therapeutic dose.[39]

In a pivotal phase 3 trial in Japan, Chiba et al showed that a single injection of condoliase (1.25 U) significantly improved worst leg pain at Week 13 vs placebo in 163 patients with radicular leg pain secondary to LDH. Condoliase demonstrated an early and durable treatment effect, with significant improvements in worst leg pain (vs placebo) beginning at Week 2 and sustained for the remainder of the study, until Week 52. Responder rate, defined as ≥50% improvement in worst leg pain at Week 13, was significantly greater with condoliase (72%) than placebo (51%). Condoliase was also associated with significantly greater improvements in neurological findings on the SLR test,

disability on the ODI, and the SF-36 physical component score (PCS), all of which were sustained until Week 52. Corresponding to the improvements in LDH symptoms, condoliase was associated with significantly greater reductions in herniated mass volume, intervertebral disc volume, and disc height at Weeks 13 and 52 compared with placebo.[47]

Both the phase 2/3 and phase 3 Japanese clinical trials demonstrated that condoliase (1.25 U) was well-tolerated in adults with LDH-associated radicular leg pain.[39,47] Only one serious AE, exacerbation of low back pain, was considered possibly related to condoliase, occurring in the phase 3 trial. In both trials, the most common AE in the condoliase group was back pain (37%), all of which was mild or moderate in severity, typically occurred within 1 week of administration, and resolved within 1 month. No patient developed anaphylactic shock in either trial, and allergy-like symptoms occurred infrequently (4–5% with condoliase 1.25 U), were moderate in severity, and resolved following treatment with oral antihistamines and steroid ointments. Condoliase is a foreign protein, so signs of hypersensitivity should be monitored. Neither of the 2 Japanese clinical trials observed an elevation in the serum level of anticondoliase IgE antibody titer. In both trials, the condoliase group had a higher incidence of Modic type 1 change and disc height reduction (≥30%) vs placebo, with a dose-response relationship observed in the phase 2/3 trial. Importantly, imaging findings were not accompanied by an increase in the incidence of leg or back pain.[39,47] Following the successful phase 3 clinical trial in Japan, the Japanese Ministry of Health, Labour and Welfare approved condoliase (1.25 U; intradiscal injection; Seikagaku Corporation, Tokyo, Japan) for the treatment of LDH in 2018.[48]

Real-World Evidence from Japan

A follow-up study of the Japanese phase 2/3 and phase 3 clinical trials, as well as numerous observational studies, further support the effectiveness and tolerability of condoliase for LDH-associated radicular leg pain. A long-term analysis of patients from the Japanese clinical trials further demonstrated the ability of condoliase to obviate or delay the need for surgery and did not reveal any new safety concerns >1 year after injection. The 1- and 6-year postinjection surgical intervention rates for condoliase were only 8.5% and 13.4%, respectively.[49] The rate of revision discectomy is similar by comparison, approximately 10% at a mean of 10.5 months after primary surgery.[50]

Recently, a single-arm meta-analysis calculated the effective treatment rate, defined as the proportion of individuals with ≥50% pain improvement on the VAS or numeric rating scale, based on 9 studies, including the 2 RCTs and 7 observational studies of condoliase. In a total of 634 patients with 3- to 12-month follow-up, the total effective treatment rate of condoliase was 78%. An analysis of 10 condoliase studies showed that the overall rate of adverse events was 4%.[51] Collectively, longer-term clinical trial follow-ups and real-world evidence from Japan suggest that condoliase may allow patients who have inadequate response to conservative treatments to avoid surgery.

US Phase 3 Discovery Trial

The safety and efficacy of condoliase has been evaluated in several clinical trials conducted in the US and one in the US and Europe. The initial US phase 3 clinical trial (NCT01941563) of condoliase in 385 patients with LDH did not meet its primary endpoint. The Discovery 6603 study (NCT03607838) was a phase 3, randomized, double-blind, sham-controlled study evaluating the efficacy and safety of a single intradiscal injection (1.25 U) of condoliase compared to sham injection in 352 adults with LDH-associated radicular leg pain.[25] Eligible participants were 30 to 70 years of age, had contained posterolateral LDH confirmed by MRI, and had inadequate improvement in pain despite ≥6 weeks of conservative treatment.

Consistent with the 2 Japanese clinical trials,[39,47] the condoliase group showed significantly greater improvements in worst leg pain at Week 13 compared with the sham control group, meeting the trial's primary endpoint.[25] Trends in treatment group differences in secondary endpoints consistently favored condoliase. The condoliase group showed numerically greater improvements in ODI vs the sham group at all timepoints. In addition, participants treated with condoliase were more likely to report a 50% improvement in their worst leg pain and more likely to have a negative SLR test (≤70°) at both Week 13 and Week 52. Corresponding to the improvement in clinical symptoms, condoliase treatment resulted in numerically greater reductions in herniation volume and intervertebral disc volumes vs sham at Weeks 13 and 52. Post-treatment surgery for LDH at the same level of injection was twice as frequent in the sham group (6.4%) vs the condoliase group (3.0%).[25]

Condoliase was well tolerated, and no SAEs were considered treatment related. Condoliase was associated with a higher incidence of Modic Type 1 classifications and ≥30% reductions in disc height vs sham. The incidence of Modic Type 2 classifications did not differ by treatment group, and no Modic Type 3 classifications were reported. While changes in imaging findings occurred more frequently in the condoliase group vs sham, these changes were not associated with leg or back pain.[25] Collectively, the results of the clinical trials and RWE on condoliase support its therapeutic potential for radicular pain associated with LDH.

Other Chemonucleolytic Therapies in Clinical Development

Several other chemonucleolytic therapies are already in use or in various stages of clinical development outside the US (Table 1). Radiopaque gelified ethanol Discogel (Gelscom SAS, France) has been on the European market since 2007 and re-obtained a Conformité Européenne (CE) mark in 2017. In addition to ethyl alcohol, gelified ethanol contains ethyl cellulose, which increases the viscosity of the alcohol solution, and tungsten, a radio-opaque element to allow radiological monitoring following injection.[52,53] Gelified ethanol is thought to degrade the proteoglycans and GAGs of the nucleus pulposus through molecular scission, leading to a loss of water-retaining capacity, dehydration, and chemical decompression of the disc.[52,53] One observational study of gelified ethanol in patients with LDH who failed conservative management and were unresponsive to oxygen-ozone chemonucleolysis reported a success rate of 75%,[53] while another study found a 91% success rate in patients treated with both gelified ethanol and intra-articular steroids.[54] In contrast, Léglise et al reported high rates of treatment failure in a small retrospective study of patients with LDH treated with gelified ethanol, possibly due to high rates of Modic 2 MRI signals.[55]

Most recently, in a retrospective study of the largest population of patients with LDH treated with gelified ethanol alone (N=71), Marcia et al found improvements in pain (VAS) and ODI score at 12 months follow-up.[52] Gelified ethanol treatment was also associated with a reduction in analgesic drug use from 70% pretreatment to 30% 12 months after treatment. Gelified ethanol showed a favorable safety profile with 1 asymptomatic complication of extravasation.[52] In accordance with EU Medical Device Regulation (MDR), a postmarket clinical follow-up (PMCF) study assessing the long-term efficacy and safety of gelified ethanol in comparison with intradiscal steroid (Hydrocortancyl 2,5 Pour Cent) in patients with lumbar discogenic pain (N=83) is ongoing in France (NCT03415828). Prospective, randomized studies are needed to further understand the risks and benefits of gelified ethanol.

First introduced in the 1980s in Italy,[56] ozone therapy has re-emerged as another potential LDH treatment that is less invasive than surgery. Following injection, unstable ozone is thought to react with proteoglycans and GAGs in the nucleus pulposus, inducing oxidation and disruption of the configuration of constituent macromolecules (eg, galactose, glucuronic acid, glycine).[56] As a consequence, the size of the herniated disc is reduced, relieving pressure on the nerve root and improving pain symptoms. A retrospective study in 149 patients with LDH found that intradiscal ozone treatment resulted in statistically significant improvements in pain on the VAS and disability on the ODI at 1- and 6-months post-procedure without serious complications.[56]

A novel oxygen-ozone generator system was developed to facilitate calibrated and sterile delivery of oxygen-ozone. This Triojection system (SpinaFX; Ontario, Canada) is not currently available for sale in the North America, the EU, or

Table 1 Chemonucleolytic Agents for LDH and Radicular Symptoms

Agent	Condition	Proposed MOA	Status/Location/NCT Number
SI-6603 (condoliase)	Radicular leg pain secondary to LDH	Enzyme degrades GAGs to reduce disc volume	• Approved in Japan • Failed US phase 3 trial (NCT01941563) • US phase 3 Discovery Study completed (NCT03607838)
Gelified ethanol	Lumbar Discogenic Pain	Ethanol dehydration of NP to reduce disc volume	• Post-CE surveillance in France (NCT03415828)
Oxygen-ozone	LDH	Oxygen-ozone reduces disc volume	• Postmarket study (NCT02525120)
Collagenase	Radicular leg pain and LDH	Collagen hydrolysis	• Randomized trial ongoing in China (NCT05330806)
STA363	Radiculopathy due to LDH	Lactic acid reduces disc volume	• Phase 1b ongoing in Poland(NCT06022263)

Abbreviations: CE, Conformité Européenne; GAGs, glycosaminoglycans; LDH, lumbar disc herniation; NP, nucleus pulposus.

the United Kingdom. The system was previously awarded a CE mark under the Medical Devices Directive (MDD) and is seeking re-registration under the MDR. In a pilot, prospective RCT in Europe (NCT02525120), Kelekis et al[57] reported that oxygen-ozone injections were non-inferior to microdiscectomy in improving radicular leg pain at 6-months follow-up in patients with single-level LDH. Both oxygen-ozone and microdiscectomy resulted in statistically significant improvements in leg pain, back pain, disability, and quality of life outcomes, and no between-group differences were observed. Notably, at 6-months follow-up, 71% of patients who received oxygen-ozone were able to avoid microdiscectomy and the attendant risks of surgery. Oxygen-ozone injections were associated with faster procedure time and shorter discharge time compared with microdiscectomy.[57] Ozone therapy may be used in conjunction with steroid injections or radiofrequency thermoregulation.[56]

Collagenase-based chemonucleolytic therapies were investigated in the 1980s in the US, and more recently have been re-explored in Asia.[36] Collagenase is believed to hydrolyze collagen fibers in the nucleus pulposus, thereby reducing the volume of the disc and relieving nerve root compression.[58] Through its nonspecific mechanism of action, collagenase is predicted to target not only the nucleus pulposus, but also the surrounding tissues including the annulus fibrosus and potentially the spinal nerves.[36] Indeed, several reports found that collagenase produced increased postoperative pressure that was associated with an increased risk of nerve root damage and aggravated pain.[59] Two retrospective studies observed that a lower dose of collagenase in conjunction with radiofrequency thermoregulation was effective in treating LDH at 3 months[59] and 10 years and produced few complications.[58] A meta-analysis evaluating the treatment success of chymopapain, condoliase, and collagenase found similar rates of treatment success across therapies, but a numerically higher rate of proceeding to surgery with collagenase (15% vs 12% chymopapain, 13% condoliase).[36] An ongoing randomized trial (NCT05330806) in China is comparing collagenase chemonucleolysis to percutaneous endoscopic lumbar discectomy in patients with LDH-associated radicular pain that has not improved with conservative therapy.

A chemonucleolytic treatment in early clinical development for chronic disc herniation is STA363 (Stayble; Gothenburg, Sweden), lactic acid mixed with the contrast agent Iohexol. STA363 was first investigated in patients with degenerative disc disease, wherein phase 1 and 2 studies showed a volume reduction in the intervertebral disc following STA363 injection. Preclinical studies had previously demonstrated that a high lactate concentration induced the degradation of GAGs in rat nucleus pulposus cells.[60] Similarly to chymopapain, STA363 is administered as a one-time injection and is thought to reduce disc volume and thus alleviate nerve root compression and relieve radicular pain. A phase 1b study (NCT06022263; estimated N=24) is ongoing in Poland to evaluate the safety and tolerability of intradiscal injection of STA363 for LDH.

Limitations of Chemonucleolytic Therapies

Chemonucleolytic therapies have several limitations, primarily related to target specificity and uncertainty on long-term outcomes. Inherent to their nonspecific mechanisms of action, gelified ethanol, oxygen-ozone, and collagenase injections all lack target specificity for the nucleus pulposus. Through this potential for nonspecific action, intradiscal injections of these treatments may risk disrupting the integrity of the surrounding tissues that support the disc, including the annulus fibrosus, facet joints, or the spinal nerves themselves (Figure 2). To address these limitations, different treatment methods have been explored, such as injecting collagenase in conjunction with radiofrequency thermoregulation or an injection system for oxygen-ozone. The efficacy and safety of these updated methods for chemonucleolytic therapies will need to be assessed in prospective RCTs. The target specificity of condoliase for nucleus pulposus GAG components differentiates it from other chemonucleolytic agents.

In addition, there is a paucity of data on long-term outcomes (≥10 years) of chemonucleolysis and its impact on spinal structures. Inherent to the mechanism of action of reducing the volume of the herniated disc to relieve nerve root compression, chemonucleolytic agents are expected to produce disc height loss and imaging changes. For example, in accordance with its mechanism of action, chemonucleolysis with condoliase has been shown to produce reductions in disc height and Modic changes, neither of which was associated with clinical symptoms.[24] One small study suggested that the decrease in disc height following condoliase administration may be transient, with some patients showing slight recovery in disc height 1 year after injection.[61] However, discectomy is also associated with structural and imaging changes, including disc height loss, Modic changes, and endplate degeneration.[62,63] While there is some evidence that

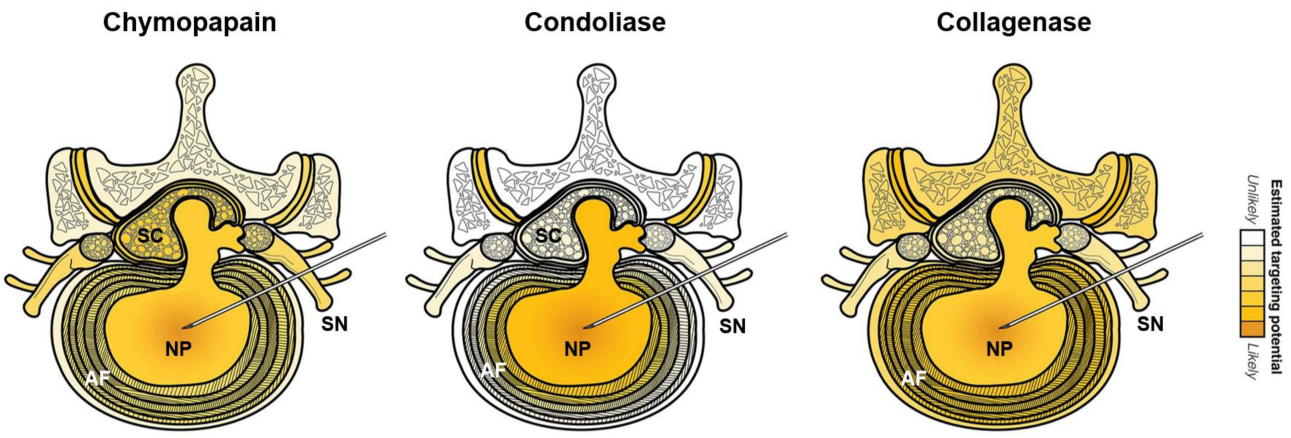

Figure 2 Predicted targeted tissues for the different agents. Adapted from Schol J, Ambrosio L, Tamagawa S et al. Enzymatic chemonucleolysis for lumbar disc herniation—an assessment of historical and contemporary efficacy and safety: a systematic review and meta-analysis. Sci Rep. 2024; 14, 12846. Creative Commons Attribution 4.0 International License.[36]
Abbreviations: AF, annulus fibrosus; NP, nucleus pulposus; SC, spinal cord; SN, spinal nerves.

Modic changes do not have a significant effect on clinical outcomes from spinal surgery,[23,64] the clinical significance of disc height loss and Modic changes is not yet understood.

Conclusions

Patients with persistent radicular pain due to LDH have few options aside from surgery to directly relieve pressure on the spinal nerves. Widely used in the US before its discontinuation in 1999, chemonucleolysis has re-emerged as a less invasive treatment than surgery for patients who do not respond adequately to conservative management. Several chemonucleolytic agents that were historically used to treat LDH, including gelified ethanol, collagenase, and oxygen-ozone, are being re-explored in Europe and Asia. While these agents have demonstrated effectiveness in improving pain, they have low substrate specificity and may spill over to adjacent structures in the spinal canal. The novel chemonucleolytic enzyme condoliase, with target specificity for nucleus pulposus components, has demonstrated a favorable safety profile in Japan since 2018. Condoliase may fulfill the current unmet need for a nonsurgical treatment that addresses the underlying nerve impingement associated with LDH. The re-emergence of chemonucleolysis, including targeted options like condoliase, are expected to improve the treatment paradigm for LDH, potentially allowing more patients to avoid or delay surgery.

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