Condoliase for lumbar disc herniation

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Percutaneous chemonucleolysis with condoliase has been available for painful lumbar disc herniation since 2018 in Japan.

In the 1980s, chemonucleolysis with chymopapain, a protease, was widely used as the intermediate treatment between conservative therapy and surgical therapy in Western countries. However, since chymopapain was withdrawn from the market in 2002 for non-scientific commercial reasons, chemonucleolysis has not been a therapeutic option for LDH. Condoliase (chondroitin sulfate ABC endolyase), a glycosaminoglycan-degrading enzyme, was approved by the drug regulatory authority in Japan as a newer intradiscal therapy for LDH after clinical studies conducted in Japan demonstrated efficacy and safety for patients with LDH [1)]

Condoliase as a first-line treatment option ahead of surgical treatment for LDH is superior, from a cost perspective to surgical treatment from the beginning. Condoliase is also a cost-effective alternative to non-surgery conservative treatment [2)].

Multicenter, randomized, double-blind, dose-finding studies

Patients between 20 and 70 years of age with unilateral leg pain, positive findings on the straight leg raise test, and LDH were recruited. All eligible patients were randomly assigned to receive condoliase (1.25, 2.5, or 5 U) or placebo. The primary end point was a change in the worst leg pain from

preadministration (baseline) to week 13. The secondary end points were changes from baseline in the following items: worst back pain, Oswestry Disability Index (ODI), SF-36, and neurological examination. For pharmacokinetic and pharmacodynamic analyses, plasma condoliase concentrations and serum keratan sulfate concentrations were measured. The safety end points were adverse events (AEs) and radiographic and MRI parameters. Data on leg pain, back pain, abnormal neurological findings, and imaging parameters were collected until week 52. RESULTS A total of 194 patients received an injection of condoliase or placebo. The mean change in worst leg pain from baseline to week 13 was -31.7 mm (placebo), -46.7 mm (1.25 U), -41.1 mm (2.5 U), and -47.6 mm (5 U). The differences were significant at week 13 in the 1.25-U group (-14.9 mm; 95% CI -28.4 to -1.4 mm; p = 0.03) and 5-U group (-15.9 mm; 95% CI -29.0 to -2.7 mm; p = 0.01) compared with the placebo group. The dose-response improvement in the worst leg pain at week 13 was not significant (p = 0.14). The decrease in the worst leg pain in all 3 condoliase groups was observed from week 1 through week 52. Regarding the other end points, the worst back pain and results of the straight leg raise test, ODI, and SF-36 showed a tendency for sustained improvement in each of the condoliase groups until week 52. In all patients at all time points, plasma condoliase concentrations were below the detectable limit (< 100 μU/ml). Serum keratan sulfate concentrations significantly increased from baseline to 6 hours and 6 weeks after administration in all 3 condoliase groups. No patient died or developed anaphylaxis or neurological sequelae. Five serious AEs occurred in 5 patients (3 patients in the condoliase groups and 2 patients in the placebo group), resolved, and were considered unrelated to the investigational drug. Severe AEs occurred in 10 patients in the condoliase groups and resolved or improved. In the condoliase groups, back pain was the most frequent AE. Modic type 1 change and decrease in disc height were frequent imaging findings. Dose-response relationships were observed for the incidence of adverse drug reactions and decrease in disc height. CONCLUSIONS Condoliase significantly improved clinical symptoms in patients with LDH and was well tolerated. While all 3 doses had similar efficacy, the incidence of adverse drug reactions and decrease in disc height were dose dependent, thereby suggesting that 1.25 U would be the recommended clinical dose of condoliase. Clinical trial registration no.: NCT00634946 (clinicaltrials.gov) [3].

Case series

Ohtonari et al. investigated clinical and radiographic outcomes three months after the administration because secondary surgical removal is most required during this period for insufficient pain relief, and analyzed whether the differences in intradiscal injection areas affected the clinical outcomes. They retrospectively investigated 47 consecutive patients (males, 31; median age, 40 years) three months after the administration. Clinical outcomes were evaluated using the Japanese Orthopaedic Association Back Pain Questionnaire (JOABPEQ), a visual analog scale (VAS) score for low back pain, and VAS scores for pains and numbness in the lower limbs. Radiographic outcomes were analyzed in 41 patients, using parameters such as mid-sagittal disc height and maximal protrusion length of herniation on MRI preoperatively and at the final follow-up. The postoperative median evaluation period was 90 days. The effective rate of low back pain based on the pain-related disorders at baseline and the last follow-up in the JOABPEQ reached 79.5%. The postoperative proportion of VAS scores recovery ≥ 2 points and ≥ 50% for pains in the lower limbs were 80.9% and 66.0%, respectively, revealing satisfactory effectiveness. Preoperative median mid-sagittal disc height significantly reduced from 9.5 to 7.6 mm postoperatively. There were no significant differences in pain relief in the lower limbs by injection areas in the center and the dorsal 1/3rd near the herniation of the nucleus pulposus. Chemonucleolysis with condoliase revealed satisfactory short-term outcomes after the administration regardless of intradiscal injection areas [4].

101 patients who underwent chemonucleolysis with condoliase from January 2019 to December 2021. Patients were divided into good outcome (i.e., favorable outcome) and poor outcome (i.e., requiring additional surgical treatment) groups. Patient demographics and imaging findings were collected. Clinical outcomes were evaluated using the numerical rating scale and Japanese Orthopaedic Association scores at baseline and at 1- and 3-month follow-up. Pretreatment indicators for additional surgery were compared between the 2 groups. Results: There was a significant difference in baseline leg numbness between the good outcome and poor outcome groups (6.27 ± 1.90 vs. 4.42 ± 2.90, respectively; p = 0.033). Of the 101 included patients, 32 received a preoperative computed tomography scan. In those patients, the presence of calcification or ossification in disc hernia occurred more often in the poor outcome group (61.5% vs. 5.3%, respectively; p < 0.001; odds ratio = 22.242; p = 0.014). Receiver-operating characteristics curve analysis for accompanying calcification or ossification showed an area under the curve of 0.858 (95% confidence interval, 0.715-1.000; p = 0.001). Conclusions: Calcified or ossified disc herniation may be useful predictors of unsuccessful treatment in patients with condoliase administration [5)].

Sixty-seven patients (44 men, 23 women; mean age, 46.7 ± 18.0 years) were analyzed. Time-course changes in disc height, disc degeneration, and herniation size were assessed. For clinical outcomes assessment, visual analog scale (VAS) scores for leg and back pain and the Oswestry disability index (ODI) were obtained at baseline and the 3-month, 1-year, and 2-year follow-ups. We obtained a questionnaire from these patients at two years to assess satisfaction and recommendation. Condoliase therapy was considered to be effective in patients whose VAS score for leg pain improved by ≥ 50% at 2 years from baseline and who did not require surgery.

Results: Condoliase therapy was effective in 51 patients (76.1%). Eight patients (11.9%) required surgery due to ineffectiveness of the therapy. Condoliase therapy was ineffective in five out of six patients with a history of discectomy. The ODI and VAS scores for leg and back pain significantly improved from three months to two years. Of the patients, 80% satisfied with their outcomes, and 85% recommended this therapy. Progression of disc degeneration was observed in 57.1% of patients at three months; however, 30% recovered to baseline at two years. The mean disc height decreased at three months, but recovered slightly at one year and remained stable until two years. No recurrent disc herniation was observed.

Conclusions: Chemonucleolysis with condoliase was effective in 78% of patients with LDH for 2 years. Chemonucleolysis-induced disc degeneration was slightly recovered and maintained for two years post-injection. This treatment resulted in high patient satisfaction and recommendations [6)].

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137 LDH patients treated through condoliase at four Japanese institutions and assessed its effectiveness among different age categories on alleviation of visual analog scale (VAS) of leg pain, low back pain and numbness, as well as ODI and JOA scores. Moreover, we divided them into either a “group-A” category if a ≥50% improvement in baseline leg pain VAS was observed or “group-N” if VAS leg pain improved <50%. Next, we assessed the differences in clinical and demographic distribution between group-A and group-N. Results: Fifty-five patients were classified as group-A (77.5%) and 16 patients were allocated to group-N (22.5%). A significant difference in Pfirrmann classification was found between both cohorts, with grade IV suggested to be most receptive. A posterior disc angle > 5° was also found to approach statical significance. In all age groups,

average VAS scores showed improvement. However, 75% of adolescent patients showed deterioration in Pfirrmann classification following treatment. Conclusions: Intradiscal condoliase injection is an effective treatment for LDH, even in patients with large vertebral translation and posterior disc angles, regardless of age. However, since condoliase imposes a risk of progressing disc degeneration, its indication for younger patients remains controversial [7].

Medical records and radiographic findings were reviewed retrospectively for 127 patients with LDH (88 male, 39 female, mean age: 46.6 ± 17.1 years, mean follow-up: 9.8 ± 7.8 months) who underwent chemonucleolysis with intradiscal condoliase injection at our center since September 2018. Condoliase (1.25 U/mL; 1 mL volume) was injected toward the middle of the affected intervertebral nucleus pulposus using a 21-gauge disc-puncture needle.

Results: Cases in which the Pfirrmann grade did and did not progress in the 3 months after the injection were included in groups P (progression, n = 49) and NP (non-progression, n = 78), respectively. Logistic regression analysis of progression of Pfirrmann grade post-injection showed significant associations with age <40 years (p = 0.013, odds ratio (OR): 3.69, 95% confidence interval (CI): 1.32-10.31), Pfirrmann Grade II or III at baseline (p = 0.021, OR: 3.51, 95% CI: 1.24-9.64), and a high-intensity MRI signal in the herniation (p = 0.047, OR: 2.97, 95% CI: 1.03-8.87). Patients in group P had significantly higher rates of disc height decrease ≥20%, reduced herniated disc size, and improved VAS for pain, but both groups had significant decreases in pain. No cases had an anaphylactic shock or neurologic sequelae.

Conclusions: These results show the safety and efficacy of chemonucleolysis with condoliase for treatment of painful LDH. Progression of Pfirrmann criteria on MRI at 3 months after injection was significantly associated with an improved clinical outcome [8].

Seventy patients (85.4%) were classified into the effective (E) group and 12 patients (14.6%) into the less-effective (L) group. Surgical treatment was required in four patients. No severe adverse complications were reported; 41.3% of the patients developed disc degeneration of Pfirrmann grade 1 or more at the injected disc level. Univariate analysis revealed that young age (p = 0.036), without history of epidural or nerve root block (p = 0.024), and injection into the central portion of the intervertebral disc (p = 0.014) were significantly associated with clinical effectiveness. A logistic regression analysis revealed that injection into the central portion of the intervertebral disc (p = 0.049; odds ratio, 4.913; 95% confidence interval, 1.006-26.204) was significantly associated with clinical effectiveness.

Conclusions: Chemonucleolysis with condoliase is a safe and effective treatment for painful LDH; 85.4% of the patients showed improvement after the treatment without severe adverse events. To obtain the best outcome, condoliase should be injected into the center of the intervertebral disc [9].

Forty-seven patients (20 women, 27 men; mean age 48 years) were included. The herniation level was L2/3 in one patient, L3/4 in two, L4/5 in 23, and L5/S1 in 21. Median symptom duration was 8 months. The mean VAS and ODI improved significantly from the baseline to 3-month follow-up (p < 0.01). Group E included 33 patients (70.2%) and group I included 14, three of whom had a history of

discectomy. The rates of spondylolisthesis and posterior intervertebral angle ≥5° were significantly higher in group I than in group E. However, the rates of trans-ligamentous type and herniation with high signal intensity on T2-weighted images (highT2) were significantly higher in group E. Reduction of disc herniation was more frequently observed in group E.

Conclusions: Condoliase injection resulted in significantly improved symptoms in patients with LDH. Condoliase therapy was less effective for patients with a history of discectomy, spondylolisthesis, or those with a posterior intervertebral angle ≥5°, while trans-ligamentous type and high T2 herniation were associated with increased efficacy [10)]

A total of 52 patients (mean age, 45.0 years) were enrolled and classified according to whether the injection was effective (E group, n=40, 76.9%) or less effective (L group, n=9, 17.3%). Three patients (5.8%) underwent herniotomy for residual pain within 6 months of the injection. There were no severe adverse events. Reduction of herniation was seen on MRI more often in the E group than in the L group. The effectiveness in patients with transligamentous LDH was similar to that in patients with subligamentous LDH. High-intensity signal change in the area of LDH on pretreatment T2-weighted MRI was a significant predictor of successful leg pain relief.

Conclusions: An intradiscal condoliase injection was a safe and effective treatment for painful radiculopathy caused by LDH. Leg pain was more likely to improve in patients with high-intensity signal change in the area of LDH before treatment [11)].

In total, 84 patients were recruited (52 men, 32 women; mean age, 44.2 ± 17.1 [16-86 years]). The duration of illness was 6.7 ± 6.8 (1.5-30) months. All patient-based outcomes significantly improved at 4 weeks after the administration compared with pretreatment. The intervertebral disc height decreased significantly at four weeks after condoliase administration compared with that before administration. Progression of intervertebral disc degeneration occurred in 50% of the patients. Eleven patients underwent herniotomy due to poor treatment effects. Moreover, treatment in 77.4% of the patients was considered effective. A logistic regression analysis revealed that L5/S1 disk administration ($p = 0.029$; odds ratio, 5.94; 95% confidence interval, 1.20-29.45) were significantly associated with clinical effectiveness.

Conclusions: Condoliase disk administration improved pain and quality of life over time. Condoliase disk administration was more effective in L5/S1 intervertebral administration [12)].

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47 patients who received condoliase, 34 were enrolled in this study. The mean age of the patients was 33 years. The average duration since the onset of disease was 8.6 months. We evaluated patients' low back and leg pain using a numerical rating scale (NRS) score at two time points (before therapy and 3 months after therapy). We divided the patients into two groups (good group (G): NRS score improvement ≥ 50%, poor group (P): NRS score improvement < 50%). The parameters evaluated were age, disease duration, body mass index (BMI), and positive or negative straight leg raising test results. In addition, the loss of disc height and preoperative radiological findings were evaluated. Results: In terms of low back and leg pain, the G group included 9/34 (26.5%) and 21/34 (61.8%) patients, respectively. Patients' age (low back pain G/P, 21/36.5 years) was significantly lower in the G group for low back pain ($p = 0.001$). High-intensity change in the protruded nucleus pulposus

(NP) and spinal canal occupancy by the NP ≥ 40% were significantly high in those with leg pain in the G groups (14/21, p = 0.04; and 13/21, p = 0.03, respectively). Conclusions: The efficacy of improvement in leg pain was significantly correlated with high-intensity change and size of the protruded NP. Condoliase was not significantly effective for low back pain but could have an effect on younger patients [13)].

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42 patients with LDH who underwent intradiscal condoliase injection. Patients with and without a ≥50% improvement from baseline of leg pain at 3 months after injection were defined as responders and non-responders, respectively. Clinical features and radiological findings were compared between these groups.

Results: Of the 42 patients, 32 (76.2%) were responders and 10 (23.8%) were non-responders. Of 8 patients with a history of discectomy at the same level as LDH, 6 (75.0%) were responders. Non-responders had a significantly longer time from onset to treatment, smaller herniated volume before treatment, lower percentage reduction of herniated mass, and less intervertebral disc degeneration before treatment. There were no significant differences in LDH types (subligamentous extrusion or transligamentous extrusion types), high-intensity area within the herniation, changes in disc height, and region of condoliase injection between the two groups.

Conclusions: Intradiscal condoliase injection had a good short-term therapeutic effect in patients with LDH, including in transligamentous extrusion-type and revision cases as well as subligamentous extrusion-type cases. Administration of intradiscal condoliase injection may be most effective in patients with a larger herniated mass volume before treatment, and least effective in cases with a longer time and less intervertebral disc degeneration before treatment [14)].

A total of 82 and 81 patients received an injection of condoliase and placebo, respectively. The average changes in worst leg pain from baseline to week 13 (primary endpoint) were -49.5 mm in the condoliase group and -34.3 mm in the placebo group, and the difference of -15.2 mm was significant (95% confidence interval, -24.2 to -6.2; P = 0.001). Significant improvements were observed in the condoliase groups, compared with the placebo group, in most secondary endpoints at 1 year after administration. In the condoliase group, back pain, Modic type 1 change, and decrease in disc height were frequently reported, without any clinically relevant consequences.

Conclusion: Condoliase significantly improved symptoms in patients with LDH and was well tolerated. Condoliase is a novel and potent chemonucleolytic drug for the treatment of LDH [15)].

Case reports

It has been available for painful lumbar disc herniation since 2018 in Japan.

A 25-year-old man with a history of LDH in L4/5, who underwent transforaminal full endoscopic lumbar discectomy when he was 17 years old, complained of severe pain radiating to his left leg for 1 month. The straight leg-raising test was limited to 25° on the left side. Lumbar T2-weighted magnetic resonance imaging (MRI) showed intracanal, left-sided transligamentous disc herniation at L4/5 with

high-signal intensity. Because the conservative treatment with oral analgesics and selective left L5 nerve root block failed, the patient requested intradiscal condoliase injection instead of revision surgery. There were no adverse events reported after the condoliase treatment, and the pain radiating to the left leg improved within 2 weeks. A lumbar MRI performed 2 months after treatment revealed that the disc herniation had significantly decreased in size. The straight leg-raising test examined 3 months after treatment was negative. In this case, the disc herniation was of the transligamentous type and showed a high-signal intensity on T2-weighted MRI which could be suitably treated by condoliase injection therapy. This case report is the first to suggest that intradiscal condoliase injection could be a useful and novel conservative treatment option to treat postoperative rec-LDH [16].

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