A Phase III Multicenter Double-blind Randomized Placebo-Controlled Study of Condoliase for Treatment of Patients with Lumbar Disc Herniation

Kazuhiro Chiba, MD, PhD¹, Yukihiro Matsuyama, MD, PhD², Yoshiaki Toyama, MD, PhD³, the Japanese SI-6603 Study Group

1. Department of Orthopaedic Surgery, National Defense Medical College, Saitama, Japan
2. Department of Orthopaedic Surgery, Hamamatsu University, School of Medicine, Shizuoka, Japan
3. Department of Orthopaedic Surgery, Keio University, School of Medicine, Tokyo, Japan
Study background

**Chemonucleolysis**
- Minimally invasive treatment for LDH using enzyme, injected into intervertebral disc
- Chymopapain, proteolytic enzyme, once gained popularity as drug approved for chemonucleolysis
- Its use has declined due to serious adverse events such as anaphylaxis and paraplegia

**Condoliase**
- is enzyme that has high substrate specificity for chondroitin sulfate and hyaluronic acid, which are glycosaminoglycans (GAGs), major constituents of the nucleus pulposus
- has no proteolytic activity and adverse effects associated with chymopapain can be minimized
Clinical protocol

Study Objective
To verify superiority of condoliase to placebo and to prove its efficacy for future clinical application as chemonucleolytic drug

Study Design
- Phase III multicenter double-blind randomized placebo-controlled study
- Involving 35 institutions in Japan

Intervention
1.25 U of condoliase in 1 ml of saline or 1 ml of vehicle only (placebo) was injected intradiscally via posterolateral puncture
Clinical protocol

Inclusion Criteria

- 20-70 years
- Unilateral leg pain (VAS≥50 mm) and positive SLR test
- Single level LDH in L4/L5, L5/L6 or L5/S1
- Refractory to conservative treatment ≥ 6 weeks
- Contained herniation with intact posterior longitudinal ligament

Exclusion Criteria

- Previous lumbar surgery
- Cauda equina syndrome or rapidly-progressing neurological deficits
- Vertebral instability on lateral dynamic radiographs
- Workers compensation
Clinical protocol

Primary end point

Changes of worst leg pain (VAS) over past 24 h, from baseline to week 13

Secondary end points

- Responder rate
- VAS back pain
- Oswestry Disability Index
- SF-36
- Neurological findings
- Imaging findings
  - Hernia volume
  - Disc height index
  - Disc volume

Safety evaluation

- Adverse events
- Imaging findings
  - Disc height index
  - Intervertebral angle
  - Vertebral translation
  - Modic type change
  - Pfirrmann grade change
## Results

### Baseline Characteristics

A total of 163 subjects received either condoliase (n=82) or placebo injection (n=81). No significant difference in baseline characteristics between two groups.

<table>
<thead>
<tr>
<th></th>
<th>Condoliase (N = 82)</th>
<th>Placebo (N = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>39.5 ± 11.1</td>
<td>39.2 ± 12.4</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51 (62.2)</td>
<td>48 (39.3)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (37.8)</td>
<td>33 (40.7)</td>
</tr>
<tr>
<td><strong>Level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L4/L5</td>
<td>45 (54.9)</td>
<td>37 (45.7)</td>
</tr>
<tr>
<td>L5/S1</td>
<td>36 (43.9)</td>
<td>40 (49.4)</td>
</tr>
<tr>
<td>L5/L6</td>
<td>1 (1.2)</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td><strong>Worst leg pain (mm)</strong></td>
<td>72.4 ± 12.3</td>
<td>74.6 ± 12.5</td>
</tr>
</tbody>
</table>

Mean ± SD, No. (%)
Results

**Primary: Worst Leg Pain**

Improvement of the worst leg pain at and after week 13, and responder rate (i.e., percentage of patients with ≥50% improvement in worst leg pain) were significantly greater in condoliase group compared with placebo group.

- Treatment effect: 
  -15.2 (-24.2 to -6.2) 
  *p=0.001*

- **LSM ± 95% CI**

- **Weeks**
  - 0
  - 6
  - 13
  - 26
  - 39
  - 52

- **Change in VAS from baseline (mm)**

- **Percentage of subjects**
  - **Week 13**
    - Condoliase: 80%
    - Placebo: 50%
    - *p=0.0077*
  - **Week 52**
    - Condoliase: 80%
    - Placebo: 60%
    - *p=0.0244*

- **Improvement of the worst leg pain at and after week 13, and responder rate (i.e., percentage of patients with ≥50% improvement in worst leg pain) were significantly greater in condoliase group compared with placebo group.**

- *p<0.05 vs placebo*
Results

Secondary: Efficacy (condoliase vs placebo)

- Symptoms and signs except for back pain, physical function and QOL improved significantly better in condoliase group
- Volumes of herniated mass decreased significantly in condoliase group compared with placebo group

<table>
<thead>
<tr>
<th></th>
<th>Week 13</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference a) (95% CI)</td>
<td>Difference a) (95% CI)</td>
</tr>
<tr>
<td></td>
<td>p Value a)</td>
<td>p Value a)</td>
</tr>
<tr>
<td>Worst Back pain (mm)</td>
<td>-7.1 (-15.0, 0.8)</td>
<td>-9.4 (-17.6, -1.3)</td>
</tr>
<tr>
<td></td>
<td>0.0765</td>
<td>0.0227</td>
</tr>
<tr>
<td>SLR test b)</td>
<td>2.9 (1.5, 5.8)</td>
<td>2.2 (1.1, 4.5)</td>
</tr>
<tr>
<td></td>
<td>0.0024</td>
<td>0.0320</td>
</tr>
<tr>
<td>Hypesthesia b)</td>
<td>2.1 (1.0, 4.5)</td>
<td>2.4 (1.1, 5.3)</td>
</tr>
<tr>
<td></td>
<td>0.0522</td>
<td>0.0347</td>
</tr>
<tr>
<td>ODI</td>
<td>-5.6 (-10.7, -0.4)</td>
<td>-6.7 (-12.6, -0.9)</td>
</tr>
<tr>
<td></td>
<td>0.0355</td>
<td>0.0250</td>
</tr>
<tr>
<td>SF-36</td>
<td>5.5 (1.1, 10.0)</td>
<td>6.1 (1.0, 11.1)</td>
</tr>
<tr>
<td></td>
<td>0.0139</td>
<td>0.0186</td>
</tr>
<tr>
<td>Hernia volume (mm³)</td>
<td>-98.3 (-162.3, -34.4)</td>
<td>-117.1 (-202.6, -31.6)</td>
</tr>
<tr>
<td></td>
<td>0.0028</td>
<td>0.0076</td>
</tr>
</tbody>
</table>

a) Analysis of covariance/logistic regression (last observation carried forward)
b) Odds ratio
Results

Safety evaluation

<table>
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<tr>
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<th>Condoliase (N=82)</th>
<th>Placebo (N=81)</th>
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<tr>
<td>Serious AEs</td>
<td>4.9</td>
<td>7.4</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>0</td>
<td>6.2</td>
</tr>
<tr>
<td>Most frequent AE (Back pain)</td>
<td>36.6</td>
<td>33.3</td>
</tr>
</tbody>
</table>

% of patients; AE: adverse event

- Condoliase was well tolerated by patients and did not cause clinically important AEs.
- No significant difference in incidence of imaging findings except for disc height between the two groups and disc height changes had no clinical impact.

Image findings

<table>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Back pain (n) a)</td>
</tr>
<tr>
<td>Decrease in disc height ≥30%</td>
<td>7 (8.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Posterior angle ≥5°</td>
<td>5 (6.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Translation ≥3 mm</td>
<td>0 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>Modic type change</td>
<td>23 (28.0%)</td>
<td>2</td>
</tr>
<tr>
<td>Pfirrmann grade change</td>
<td>44 (53.7%)</td>
<td>1</td>
</tr>
</tbody>
</table>

a) Number of patients with not resolved AE (back pain) at Week 52 or Discontinuation visit
Condoliasiase is novel and potent chemonucleolytic drug providing minimally invasive treatment for lumbar disc herniation
This study was funded by Seikagaku Corporation, Tokyo, Japan

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