Non-Invasive Vagus Nerve Stimulation Improves Signs and Symptoms of Rheumatoid Arthritis

Results from a Pilot Study

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Disclosures

- Dr. Baker has received consulting fees from Vorso Corp
- The study was sponsored by Vorso Corp
Study Objectives

- To investigate the safety and efficacy of a wearable, non-invasive, auricular vagus nerve stimulation device for the treatment of rheumatoid arthritis

Vagus Nerve Stimulation: Mechanism of Action

The CNS inflammatory reflex

- Vagus nerve sensory afferents convey information about the inflammatory state to the brainstem
- After CNS integration, the vagus nerve sends efferent signals to the spleen
- These signals regulate proinflammatory macrophage cytokine production

Study Design and Statistical Analysis

- Multicenter, open-label study of 30 patients with rheumatoid arthritis
- All patients treated with non-invasive vagus nerve stimulation for 12 weeks
- Conducted in Barcelona, Spain between Dec 2018 and Jan 2020
- Patients were instructed to use the device for up to 30 minutes per day
**Key Inclusion Criteria**

- Active rheumatoid arthritis
  - Based on 2010 ACR/EULAR classification criteria
  - ≥ 4 tender and swollen joints based on a 28-joint count
  - DAS28-CRP > 3.8
  - Active synovitis detected on ultrasound and MRI
- Inadequate response to conventional synthetic DMARDs and up to one biologic DMARD

**Key Exclusion Criteria**

- History of unilateral or bilateral vagotomies
- Recurrent vasovagal syncope
- Previously implanted electrically active medical devices
  - e.g. cardiac pacemakers, automatic implantable cardioverter-defibrillators
- Significant electrocardiogram findings
Primary and Secondary Endpoints

Primary Endpoint
- DAS28-CRP at Week 12

Secondary Endpoints
- ACR 20/50/70
- Change in HAQ-DI
- Proportion of patients achieving a HAQ-DI of 0.22
- Proportion of patients achieving low disease activity and remission
- Changes in synovitis, osteitis, and bone erosion by imaging
- Change in serum cytokines
- Safety and adverse events
Subject Disposition

35 patients screened for eligibility

5 patients did not participate
Reasons for exclusion:
1 – use of more than one bDMARD
1 – did not meet ultrasound screening criteria
1 – confounding condition (osteoarthritis)
2 – eligible but chose not to participate

30 patients received and began using the device

3 patients discontinued
1 – withdrew at Week 8 (left the country)
2 – lack of efficacy (withdrew at Weeks 2 and 6)

27 patients completed 12 weeks
### Baseline Characteristics for 30 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>54.4 (10.0)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>27 (90)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>27.2 (4.8)*</td>
</tr>
<tr>
<td>Duration of disease (years), mean (range)</td>
<td>7.3 (0 – 21)**</td>
</tr>
<tr>
<td>Patients with previous exposure to bDMARD, n (%)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>DAS28-CRP, mean (SD)</td>
<td>5.3 (1.0)</td>
</tr>
<tr>
<td>Tender joint count (out of 28), mean (range)</td>
<td>12.2 (3 – 28)</td>
</tr>
<tr>
<td>Swollen joint count (out of 28), mean (range)</td>
<td>7.0 (2 – 16)</td>
</tr>
<tr>
<td>HAQ-DI, mean (SD)</td>
<td>1.6 (0.7)</td>
</tr>
<tr>
<td>Rheumatoid factor (&gt;20u/ml), n (%)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>Anti-CCP (&gt;20u/ml), n (%)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Methotrexate usage in study population, n (%)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Methotrexate dose/week (mg), mean (SD)</td>
<td>19.1 (6.1)</td>
</tr>
<tr>
<td>Glucocorticoid usage in study population, n (%)</td>
<td>19 (63)</td>
</tr>
<tr>
<td>Prednisone dose/day (mg), mean (SD)</td>
<td>7.0 (2.6)</td>
</tr>
</tbody>
</table>
Change in DAS28-CRP

Mean change in DAS28-CRP from Baseline to Week 12 was -1.40 (p<0.001)
ACR 20/50/70 Response Rates

- **ACR20:** 53%
- **ACR50:** 33%
- **ACR70:** 17%
- Non-responder imputation was used
Changes in DAS28-CRP

- Baseline vs Week 12
- Graphs showing changes in DAS28-CRP levels.
## Individual components of DAS28-CRP and ACR response criteria

<table>
<thead>
<tr>
<th>Score or Component</th>
<th>Baseline (n=30), mean (SD)</th>
<th>Week 12 (n=27), mean (SD)</th>
<th>Change (n=27), mean (SD)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28-CRP</td>
<td>5.3 (1.0)</td>
<td>3.8 (1.4)</td>
<td>-1.4 (1.2)</td>
<td>-1.9, -0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tender joints</td>
<td>12.2 (6.5)</td>
<td>4.7 (5.8)</td>
<td>-6.7 (5.4)</td>
<td>-8.8, -4.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Swollen joints</td>
<td>7.0 (3.4)</td>
<td>3.4 (3.9)</td>
<td>-3.2 (3.5)</td>
<td>-4.5, -1.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>1.6 (0.7)</td>
<td>1.1 (0.8)</td>
<td>-0.5 (0.6)</td>
<td>-0.7, -0.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patient global health assessment</td>
<td>72.2 (20.0)</td>
<td>45.3 (31.6)</td>
<td>-24.9 (31.9)</td>
<td>-37.5, -12.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Physician global health assessment</td>
<td>56.2 (16.5)</td>
<td>30.7 (25.6)</td>
<td>-24.5 (24.6)</td>
<td>-34.4, -14.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain score</td>
<td>75.2 (19.1)</td>
<td>43.3 (26.3)</td>
<td>-30.3 (28.7)</td>
<td>-41.6, -19.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>10.4 (11.6)</td>
<td>12.5 (21.3)</td>
<td>2.9 (16.1)</td>
<td>-3.5, 9.2</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Change in HAQ-DI

- HAQ-DI decreased 0.47 from Baseline to Week 12 (p<0.05)
- 56.7% of patients (17/30) achieved an overall HAQ-DI reduction of 0.22

*** p<0.001
Change in Ultrasound and MRI

**p<0.01  **p<0.01

<table>
<thead>
<tr>
<th>Score</th>
<th>Baseline mean (SD)</th>
<th>Week 12 mean (SD)</th>
<th>Change mean (SD)</th>
<th>95% CI</th>
<th>SDC</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARLOS</td>
<td>4·0 (5·6)</td>
<td>4·0 (5·7)</td>
<td>0·1 (0·2)</td>
<td>-0·02, 0·1</td>
<td>0·3</td>
<td>0·16</td>
</tr>
<tr>
<td>Erosion</td>
<td>13·6 (11·3)</td>
<td>13·6 (11·3)</td>
<td>0·0 (0·8)</td>
<td>-0·3, 0·4</td>
<td>1·8</td>
<td>0·80</td>
</tr>
<tr>
<td>Osteitis</td>
<td>3·4 (4·2)</td>
<td>3·0 (4·0)</td>
<td>-0·4 (2·5)</td>
<td>-1·6, 0·8</td>
<td>1·5</td>
<td>0·46</td>
</tr>
<tr>
<td>Synovitis</td>
<td>7·0 (4·4)</td>
<td>6·9 (4·5)</td>
<td>-0·1 (0·9)</td>
<td>-0·5, 0·3</td>
<td>1·3</td>
<td>0·63</td>
</tr>
</tbody>
</table>
### Change in Serum Cytokines

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Week 0 (Baseline)</th>
<th>Week 12</th>
<th>Week 12 – Wk 0 Paired p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N &lt; DL</td>
<td>median</td>
</tr>
<tr>
<td><strong>TNF-α</strong></td>
<td>30</td>
<td>0</td>
<td>9.2</td>
</tr>
<tr>
<td><strong>sCD25</strong></td>
<td>29</td>
<td>0</td>
<td>1887</td>
</tr>
<tr>
<td><strong>IL-10</strong></td>
<td>30</td>
<td>0</td>
<td>3.6</td>
</tr>
<tr>
<td><strong>IL-1β</strong></td>
<td>30</td>
<td>10</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>IL-12p70</strong></td>
<td>30</td>
<td>18</td>
<td>..</td>
</tr>
<tr>
<td><strong>IFNγ</strong></td>
<td>30</td>
<td>26</td>
<td>..</td>
</tr>
<tr>
<td><strong>IL-6</strong></td>
<td>30</td>
<td>1</td>
<td>6.2</td>
</tr>
</tbody>
</table>
Safety

- 4 adverse events (AEs) were reported:
  - 1 device-related AE of superficial skin abrasion
  - 2 unrelated patient falls
    - 1 due to tripping on an uneven surface
    - 1 related to underlying poor eyesight
  - 1 unrelated AE of mucous accumulation in the throat
- All AEs resolved without intervention or further sequela
- No serious AEs or deaths were reported
Compliance and Satisfaction

- Patients used the device on 94% of the days they were in the study.
- Patients used the device for 24.7 minutes/day on average.
Conclusions

- In this open-label study of non-invasive auricular vagus nerve stimulation for the treatment of rheumatoid arthritis:
  - The device was well tolerated with no serious adverse events
  - There was a high rate of patient compliance
  - The signs and symptoms of rheumatoid arthritis improved
- Further evaluation in larger, controlled studies is warranted
The trial was conducted at 6 centers in Barcelona, Spain

The investigators and the sponsor thank the patients and their families for their participation in the study

Investigators:
- Sara Marsal
- Héctor Corominas
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