Pilot Clinical Study of a Non-invasive Auricular Vagus Nerve Stimulation Device in Patients with Rheumatoid Arthritis

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BACKGROUND

Despite the clinical benefit of current pharmacological treatments for RA, only a minority of patients reach the treatment goal of remission or low disease activity[1]. Vagus nerve stimulation (VNS) via an implanted device has been shown to attenuate RA disease severity[2]. A non-invasive VNS device with comparable efficacy may prove to be a safer and more desirable treatment option for patients.

OBJECTIVES

This pilot study investigated the safety and efficacy of a wearable (non-invasive) device that attaches to the outer ear to treat RA via electrical stimulation of the auricular branch of the vagus nerve.

METHODS

Inclusion criteria

- Active RA:
  - ≥4 tender/swollen joints based on a 28-joint count
  - DAS28-CRP >3.8
  - Active synovitis detected on ultrasound and MRI
- Inadequate response to csDMARDs, or csDMARD and 1 bDMARD

Study design

- Open-label, 12-week study
- Patients used the device for up to 30 minutes daily

Primary endpoint

- Change in DAS28-CRP score at Week 12

Secondary endpoints

- Proportion of patients achieving ACR20/50/70
- Mean change in HAQ-DI
- Proportion of patients achieving a HAQ-DI MCID of at least 0.22 over 12 weeks
- Sleep scores were assessed using a visual analogue scale (0-100) at baseline and 12 weeks

Safety analysis

RESULTS

Patient disposition and baseline characteristics:

- 30 patients enrolled, 27 patients completed the 12-week protocol
- The mean age was 54.4 years, 90% were female, mean duration of disease was 7.32 years, and 4 patients had an inadequate response to at least 1 bDMARD

Primary outcome

- The mean change in DAS28-CRP from baseline to Week 12 was -1.40 ($p<0.001$; Figure 1)

Secondary outcomes

- ACR20/50/70 response rates were 53.3%, 33.3% and 16.7%, respectively (Figure 2)
- HAQ-DI change from baseline was -0.47 ($p<0.05$) at 12 weeks
- 17/30 (56.7%) patients achieved overall HAQ-DI reduction of 0.22
- VAS sleep scores were significantly improved over 12 weeks
  - Scores for trouble falling asleep, awakened by pain at night, and awakened by pain in morning decreased by 63.7%, 70.4%, and 55.6%, respectively ($p<0.01$, $n = 26$)

Safety outcomes

- 4 adverse events (AEs) were reported:
  - 1 device-related AE of superficial skin abrasion
  - 2 unrelated accidental patient falls (due to tripping on an uneven surface and underlying poor eyesight)
  - 1 unrelated AE due to mucous accumulation in the throat
- All AEs resolved without intervention or further sequela

Compliance

- Patients used the device on 93% of the days they were in the study
- Patients used the device for 24.7 minutes/day on average
- More than 1000 hours of stimulation were delivered over the entire cohort

References:

[1] Van Vollenhoven RF et al. (2012) Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 367(6):508-519.

[2] Koopman FA, et al. (2016) Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. Proc Nat Acad Sci 113:8284–9.

CONCLUSIONS

In this pilot study, auricular stimulation was well tolerated and daily use over 12 weeks resulted in clinically meaningful and statistically significant reductions in the DAS28-CRP and RA disease severity without any serious adverse events. Further evaluation in larger controlled studies is needed to confirm whether this non-invasive device might offer an alternative approach for the treatment of RA.

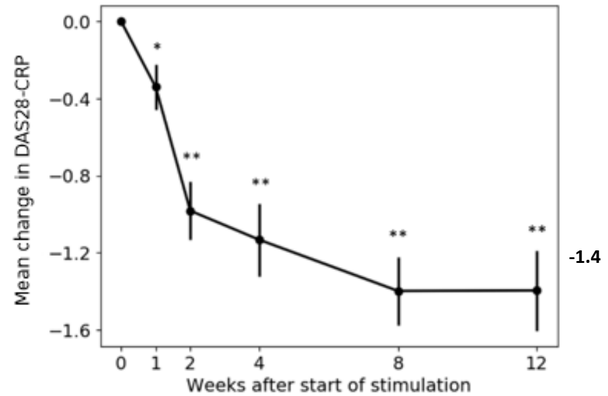

Figure 1. Mean change in DAS28-CRP score for each study visit. Error bars indicate standard error of mean. One (*) asterisk indicates $p < 0.05$ and two (**) asterisks indicate $p < 0.01$. P-values were calculated using paired two-tail t-tests.

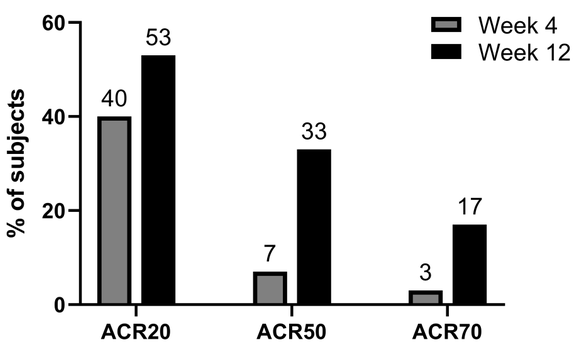

Figure 2. Percentage of all 30 patients who achieved ACR20/50/70 at week 4 (grey) and at week 12 (black). Patients who did not complete the study were deemed non-responders.

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