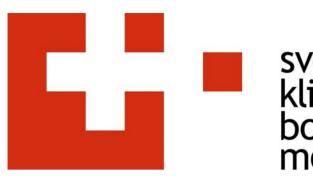
Pilot Study of Stimulation of the Cholinergic Anti-inflammatory Pathway with an Implantable Vagus Nerve Stimulation Device in Patients with Rheumatoid Arthritis





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Abstract

BACKGROUND

The inflammatory reflex regulates (Andersson U, Tracey K, Annu. Rev. its efferent arm (the Cholinergic Anti-inflammatory Pathway (CAP)), by electrical vagus nerve stimulation (VNS) reduces systemic inflammation and ameliorates disease in many acute and chronic animal models. We determined whether VNS could similarly improve clinical manifestations of rheumatoid arthritis (RA).

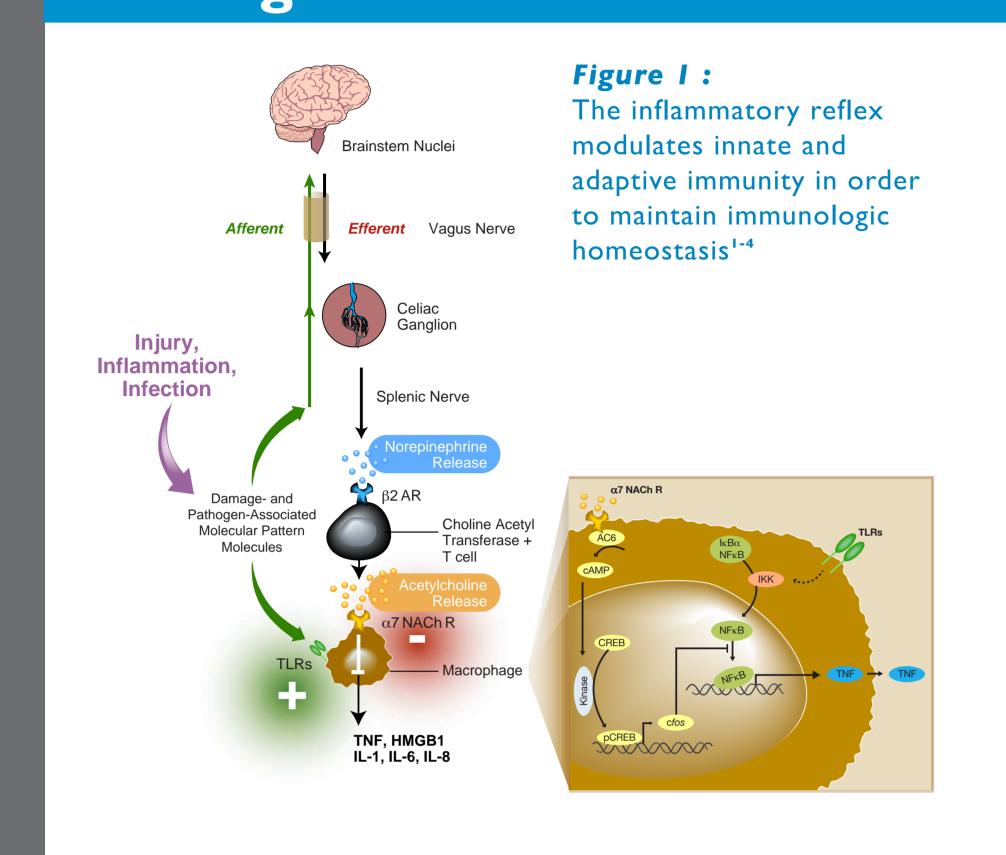
This is an open label study of patients with active RA (>/= 4 tender and 4 swollen joints (28 joint scoring). and CRP of at least 7 mg/L) despite stable methotrexate dose for 3 **Patients** (only for safety or tolerability reasons) could also be enrolled after washout. After a pre-implantation patients were surgically implanted with a Cyberonics VNS system. The device delivered the first VNS during its standard intraoperative diagnostic check sequence. Two weeks following implantation patients returned for initial in-clinic VNS. One week after the first clinic visit (day 7), patients began self-delivery of 60 second. escalated in output current intensity as tolerated, through day 28. At day 28 patients without a EULAR good or moderate response were increased to four times daily VNS. Primary endpoint results at day 42 are

RESULTS 8 patients (4 female, 7/8 RF+, 6/8 ACPA+, mean age 56 [range 39-70], mean disease duration 8 yrs [range 0.5-13]) were enrolled and implanted. Implantation and stimulation were generally well tolerated. Moderate postoperative hoarseness occurred in one patient. Pre implantation baseline values (mean, SD) were: DAS28-CRP: 6.06 (0.87), CRP: 17.5 mg/L (9.9), HAQ-DI: 1.63 (0.90). Changes at day 42 visit from values pre-implantation DAS28-CRP: -2.28 (1.65), CRP: -3.46 (17.95) mg/L , HAQ-DI: -0.44 (0.48). Similar levels of improvement were seen across all ACR core set assessments. ACR 20/50/70 response rates from pre-implantation baseline to day 42 were 75% (6/8), 50% (4/8), and 25% (2/8), respectively.

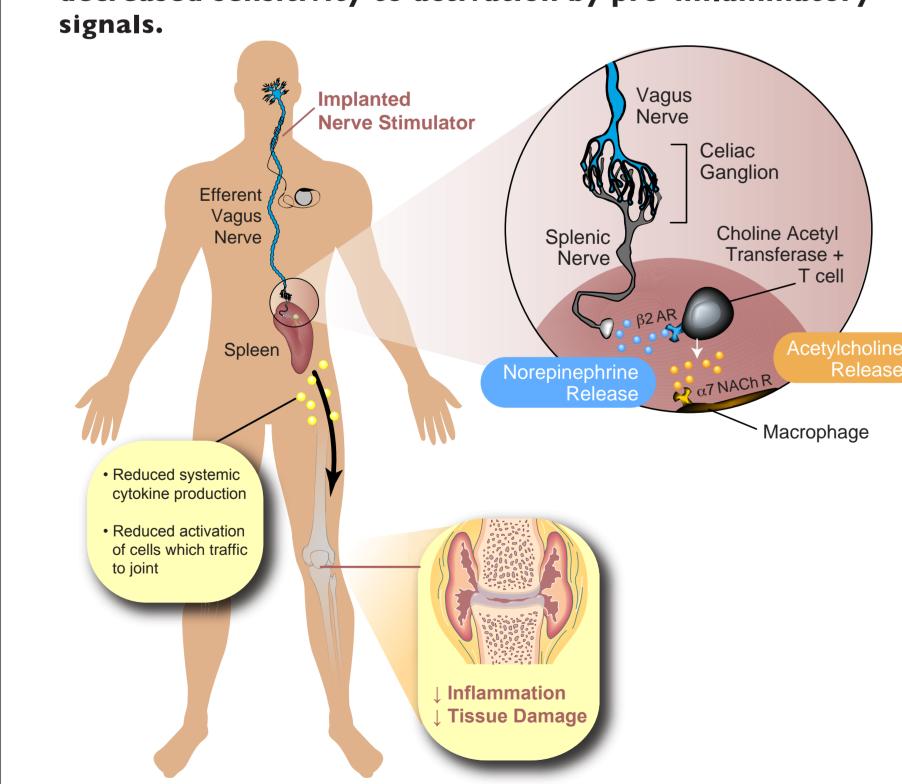
CONCLUSIONS

In this pilot study VNS was generally well tolerated and improved signs and symptoms of RA. This is the first demonstration in humans that stimulation of the CAP can favorably impact clinical manifestations of systemic inflammation. If efficacy and safety are confirmed in larger controlled studies, implantable medical devices may offer a feasible approach to the treatment of RA and other chronic inflammatory diseases.

Background



- Tissue injury, inflammation and infection are sensed both centrally and by the afferent vagus nerve and signals are relayed through brainstem vagal nuclei to the efferent
- The efferent arm of the inflammatory reflex is termed the "Cholinergic Anti-inflammatory Pathway (CAP)": Efferent neural signaling proceeds through the sub-diaphragmatic celiac ganglion to the adrenergic splenic nerve, and into
- Within splenic white pulp, splenic nerve fibers lie in close apposition to alpha 7 nicotinic acetylcholine receptor-bearing (α 7NAChR) macrophages, and a specific subpopulation of beta adrenoceptor-bearing CD4+/CD44high/CD62L low T cells which have the capacity to synthesize and release acetylcholine.
- Acetylcholine signaling induces phenotypic changes in macrophages and monocytes via α 7NAChR which results in decreased sensitivity to activation by pro-inflammatory

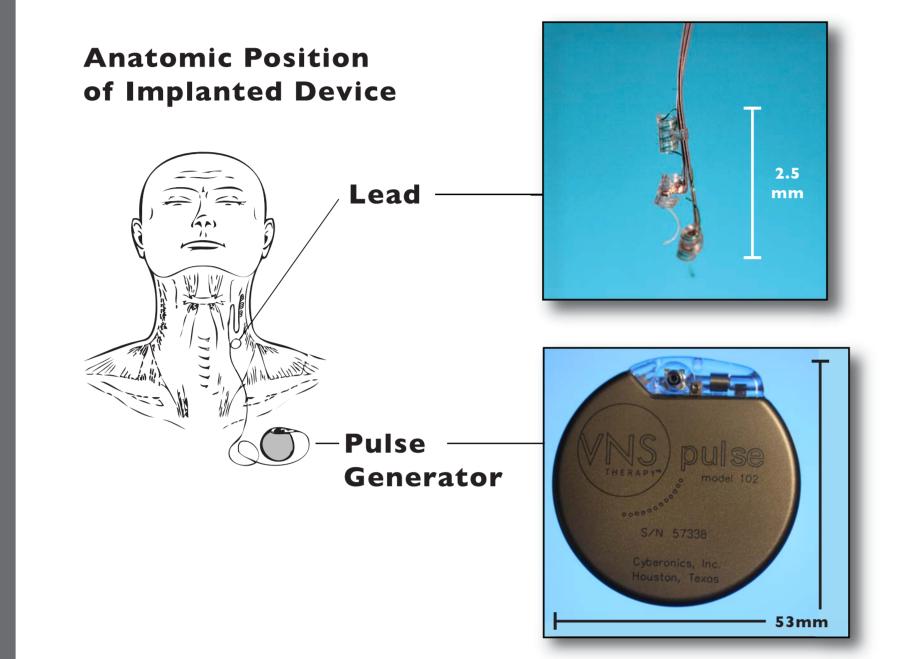


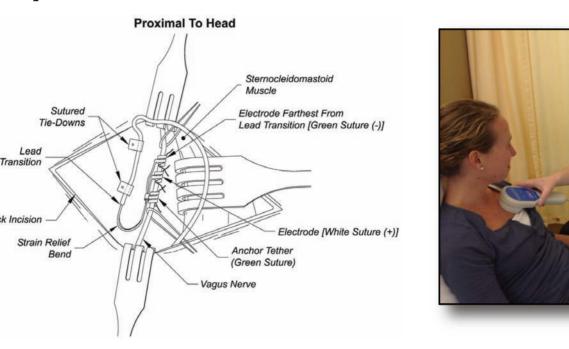
Neurostimulation of the Efferent Limb of the Inflammatory Reflex Enables a Means for Non-Pharmacologic Management of RA

- In RA and other inflammatory disorders there is epidemiological evidence for insufficient levels of parasympathetic activity, and the extent of reduction correlates inversely with disease activity3.
- Activating the CAP is effective in rodent CIA and many other acute and chronic models of inflammation³⁻⁸.
- CAP activation using an implantable neuromodulation device in RA patients should reduce production of systemic pro-inflammatory mediators and activation of immune effector cells trafficking to the inflamed joint, thereby improving clinical signs and symptoms of RA.

Methods

Figure 3: Vagus nerve stimulation was performed in this study using a commercially marketed

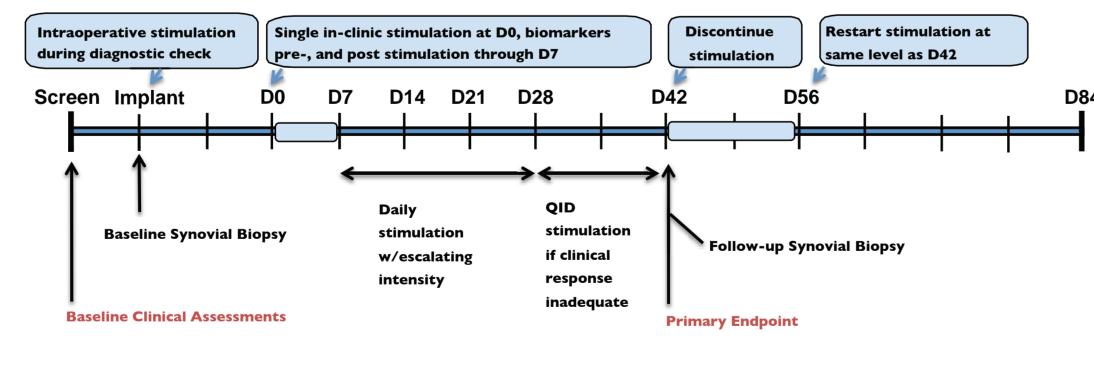






- The Cyberonics VNS[®] system has been approved for use in medically refractory epilepsy for more than 15 years, with over 60,000 patients
- Use of this device in RA is investigational: The trial was approved by the designated Ethics Committee and Competent Regulatory Authority for each site.
- Standard commercially-available devices were purchased for this study, implanted by experienced neurosurgeons as recommended by the manufacturer, and programmed according to protocol-specified algorithms by the site staff.
- At study conclusion, patients could undergo surgical removal of the device, keep the device in place but have it permanently inactivated, or continue in a long term safety extension protocol. All patients enrolled opted to continue in the extension study.

STUDY DESIGN



STUDY POPULATION

- Adult-onset rheumatoid arthritis (RA) of at least six months duration as defined by 2010 ACR/EULAR criteria
- Male or female patients 18-75 years of age Functional status I, II, or III according to ACR 1991 criteria • Active disease defined by at least 4 tender and swollen joints and CRP
- above 7 mg/L, despite at least 3 months of methotrexate at a dose of up to 25 mg orally per week • Past TNF antagonist use acceptable, but must have failed on basis of

ENDPOINTS

• Change in DAS28 (Primary)

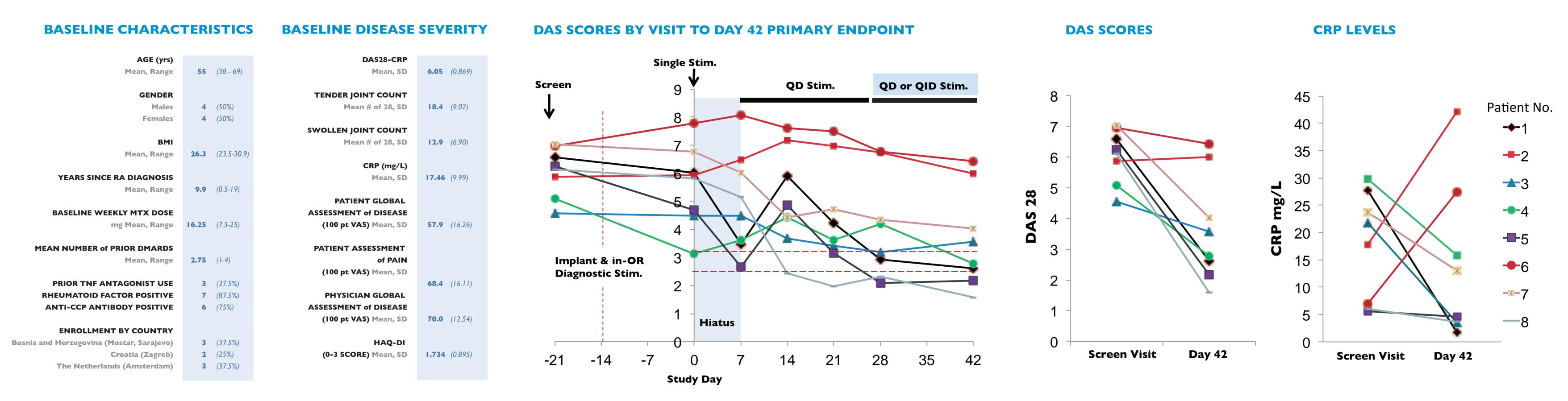
safety, and not due to lack of efficacy

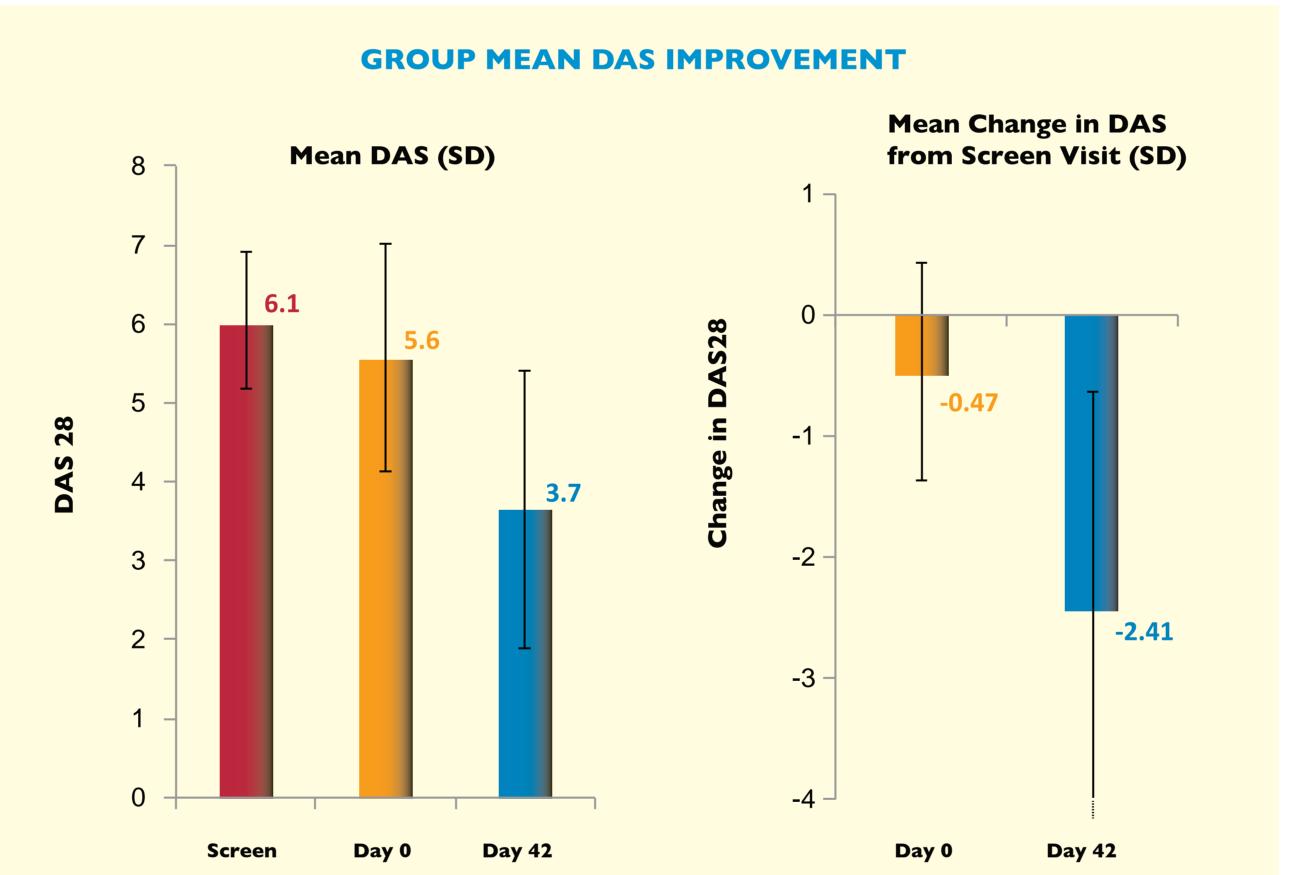
- ACR 20/50/70 Response Rate EULAR Response Rate
- EULAR Remission Rate

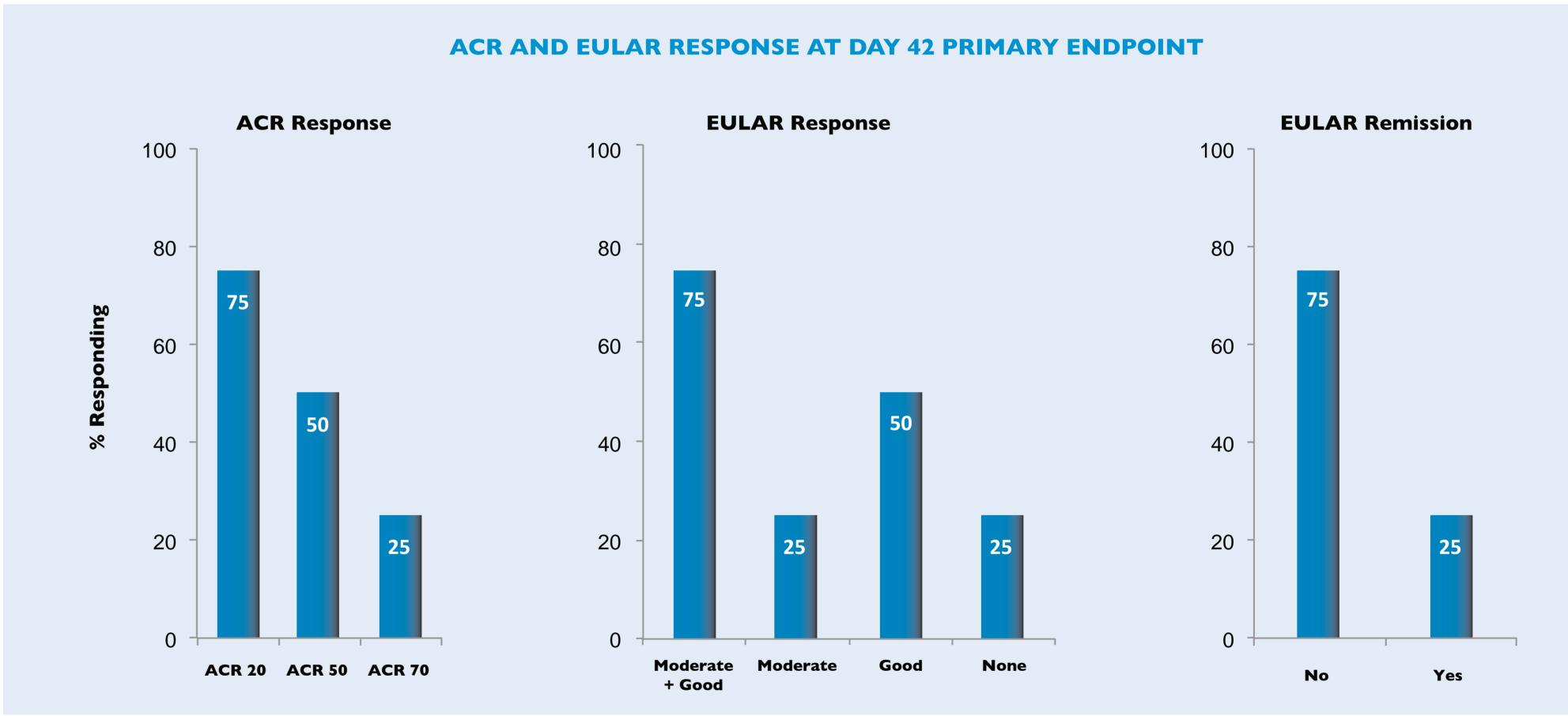
to be reported elsewhere

- Biomarkers (FACS, serum cytokines, LPS-induced TNF release assay):
- Synovial Biopsy (Immunohistochemistry, PCR): to be reported elsewhere

Results







SAFETY

No Serious Adverse Events

No Adverse Event withdrawals

- All were mild or moderate

occurred in 3 patients:

- "Tingling in scar area"

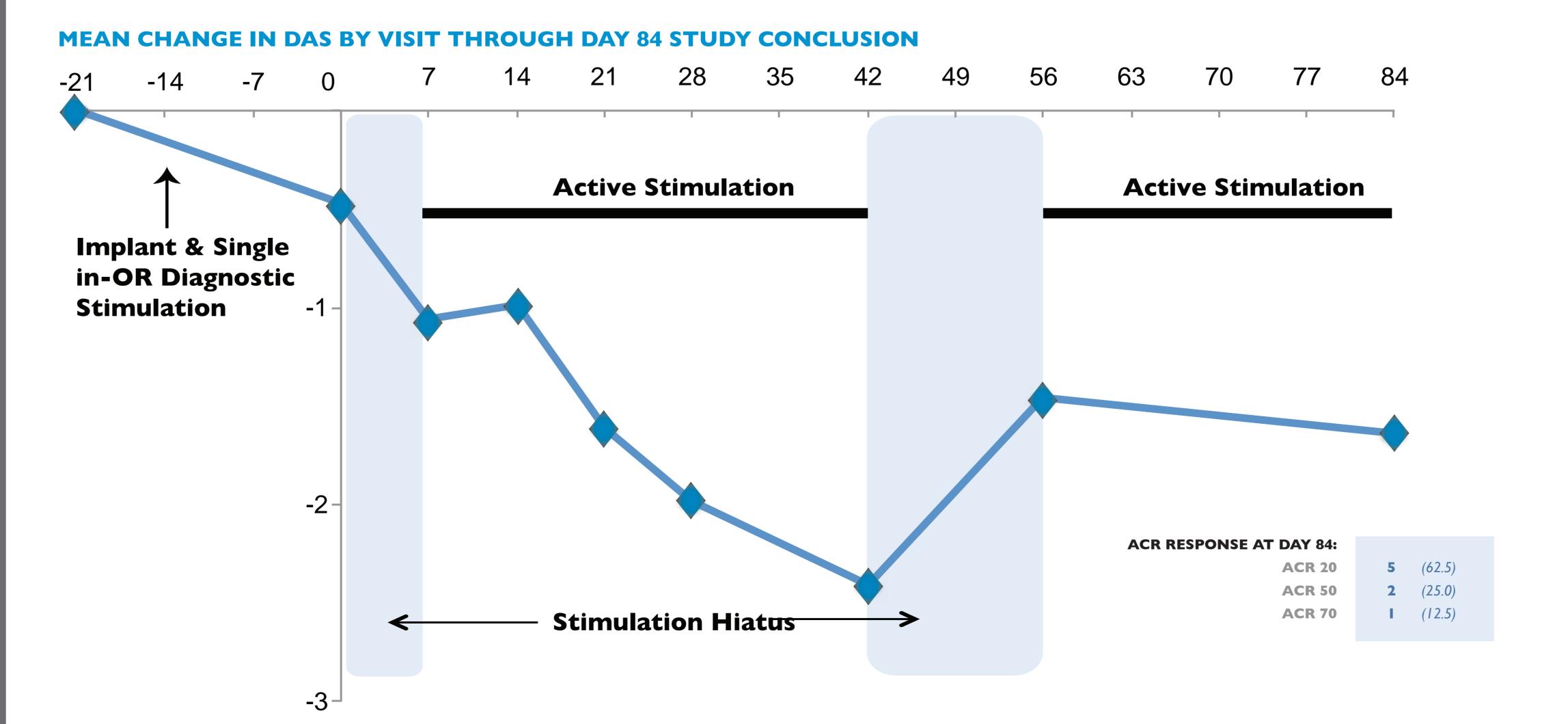
No device-related Adverse Events

A total of 21 Adverse Events occurred in 7 subjects:

Implantation procedure-related Adverse Events

- "Dry throat", "hoarseness", "dyspnea"

- "Numbness of skin on neck under jaw"



Summary & Conclusions

Summary

- Treatment resulted in significant and clinically meaningful improvement in signs and symptoms at the Day 42 primary
- DAS28 improvement of 2.41 points
- ACR 20/50/70 response rates of 75%, 50%, and 25%
- EULAR good or moderate response in 75%
- EULAR remission in 25%
- Loss of efficacy, as expected, following temporary treatment discontinuation after Day 42 visit
- Partial recapture of effect at Day 84 following re-institution of treatment
- Treatment was generally well tolerated, with an Adverse Event profile consistent with other studies using this device.

Conclusions

- This is the first clinical trial suggesting that an implantable neuromodulation device can activate the inflammatory reflex and improve clinical manifestations of RA.
- Further larger controlled studies in RA and other chronic inflammatory diseases are warranted.
- Given the relatively low one-time cost, and long expected lifespan of implantable medical devices, this approach has the potential to reduce health care expenditures in these diseases.





DISCLOSURES



SPM-005 STUDY TEAM



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