P1420 - A Clinical Trial of the Effects of Vagus Nerve Stimulation in Biologic-refractory Crohn's Disease

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ABSTRACT

INTRODUCTION

The autonomic nervous system regulates innate and adaptive immunity[1]. Activation of its efferent arm, the Cholinergic Anti-inflammatory Pathway (CAP) by electrical vagus nerve stimulation (VNS) reduces inflammation and ameliorates disease in animal models of colitis[2]. VNS has been studied in a biologic-naïve Crohn's disease (CD) population showing significant benefit[3].

AIMS and METHODS

We studied the efficacy of VNS in biologic–refractory CD patients in a clinical trial. This is an open label study of patients with active CD (CDAI 220-450, stool calprotectin 200 µg/g, and SES-CD ulcer score ≥ 2 in at least 1 segment with centrally blinded endoscopy reading. Patients refractory to biologic agents (TNF antagonists and/or vedolizumab) entered an 8 week wash out. A VNS stimulation device was implanted, consisting of a pulse generator and an electrical lead tunneled into the carotid sheath and affixed to the vagus nerve. Two weeks following implantation, stimulation was initiated (pulse width 250 microseconds, 10 Hz frequency, output current incremented by tolerability to a max of 2.0 mA, for 60 seconds). From 4 to 6 weeks the output current was increased and stimulation was increased to 5 minutes. At 8 weeks, stimulations were increased from QD to QID if CDAI remission was not achieved. The stimulation remained at this level from 8 to 16 weeks, the time point of repeat endoscopy and primary endpoint (PE).

RESULTS

So far, 5/8 patients reached the PE
(6 males, 38 years [range 21-65]). The median (IQR) CDAI decreased from 300 (271-388) to 171 (127-395), fecal calprotectin from 4708 (1996-9390) to 1153 (509-3861) µg/g, the hs-CRP from 5.95 (2.64-8.10) to 2.78 (1.45-7.13) mg/dL, and the SES-CD from 24.5 (17.1-29.0) to 19.0 (13.5-28.5). There were 3/5 patients with CDAI-100 response, 2/5 with CDAI remission, and 4/5 with reduced SES-CD. There were 9 Serious Adverse Events occurring in 5/8 patients, all of which were CD-related except for 1 patient (device-related postoperative infection).

CONCLUSIONS

VNS induced clinical and endoscopic improvement in a significant proportion of highly refractory CD patients. The trial is ongoing and additional patients will be studied.

[1] Andersson, J Exp Med 2012; 209:1057.
[2] Matteoli, Gut 2013; 62:1214.
[3] Bonaz, Neurogastoenterology, 2016; doi:10.1111.

BACKGROUND

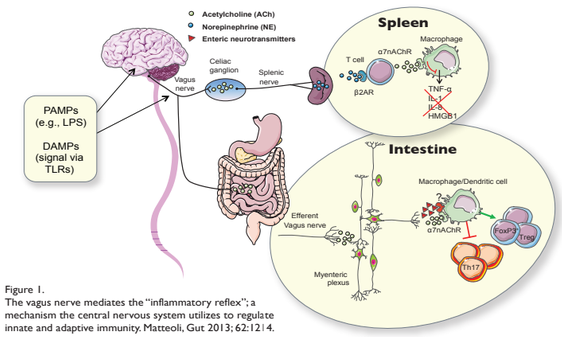


Figure 1.
The vagus nerve mediates the "inflammatory reflex"; a mechanism the central nervous system utilizes to regulate innate and adaptive immunity. Matteoli, Gut 2013; 62:1214.

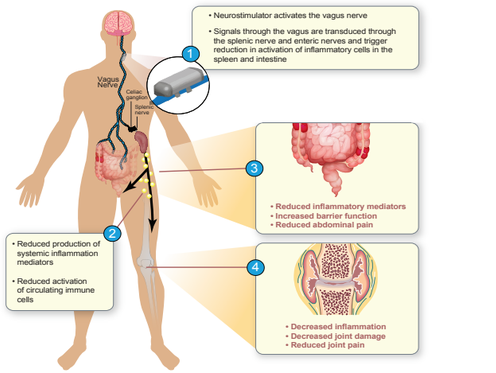


Figure 2:
Driving this reflex by using an electrically active medical device is a feasible means of treating these diseases. Levine, Bioelec Med 2014; 1:34.

- We have published our successful experience with using VNS in rheumatoid arthritis (Koopman, 2016).
- In a study with a similar device in 7 TNF antagonist-naive Crohn's patients (Bonaz, 2016), 5 of 7 had response (CDAI <150), and 2 had remission. The CDEIS response in the CDAI responders were all <5.
- We hypothesized that VNS could be effective in later stage patients who have failed conventional treatments.

METHODS

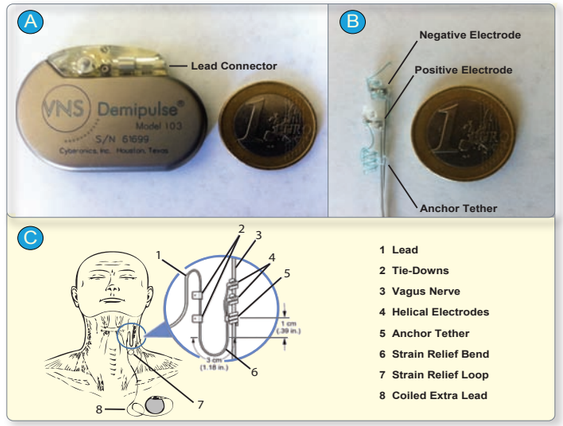


Figure 3. The Cyberonics VNS device has a pulse generator which contains a battery, controlling circuits, and the lead connector (A). It is placed on the anterior thorax subcutaneously (B). A lead (C) is tunneled up to the neck and it is implanted in the cervical vagus in the carotid sheath.

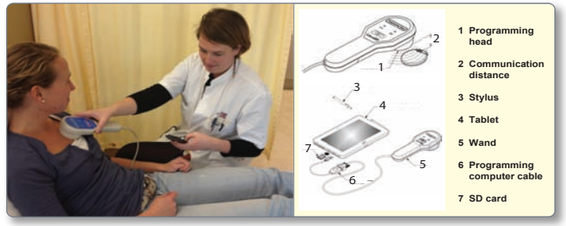
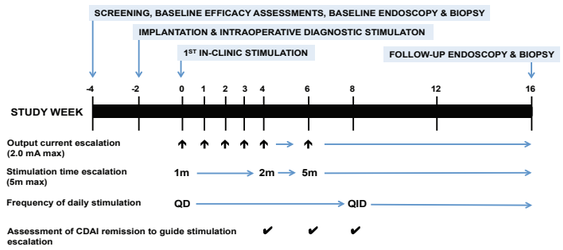


Figure 4. The programming of the Cyberonics VNS device in clinic is shown. A handheld wand transmits the telemetric information and a tablet controls the VNS system.

Figure 5. Study design



MAJOR INCLUSION CRITERIA

- Male or female subjects aged 18-75 years, inclusive
- Written informed consent prior to any of the screening procedures
- Diagnosis of Crohn's disease for more than 4 months prior to screening, with small bowel and/or colonic involvement
- Current evidence of moderately-to-severely active disease defined by a Crohn's Disease Activity Index (CDAI) score of 220 to 450, inclusive
- Serum levels of C-reactive protein (CRP) greater than or equal to 5 mg/L for the highly sensitive C-reactive protein test (hsCRP) at screening
- Simple Endoscopic Score for Crohn's Disease evaluation at baseline showing presence of a minimal ulcer score of 2 or 3 in at least 1 segment
- Levels of fecal calprotectin greater than or equal to 200 microgram/gram feces at screening
- History of inadequate response and/or intolerance or adverse events to one or more TNF-alpha inhibitors (e.g., infliximab, adalimumab, or certolizumab pegol).
- Female subjects of child-bearing potential are eligible if not pregnant, not planning to become pregnant during the course of the study, and committed to use of contraceptive methods with a failure rate of less than 1 percent per year

MAJOR EXCLUSION CRITERIA

- Celiac disease, ulcerative or indeterminate colitis, enterocutaneous, abdominal or pelvic fistulae with abscesses, or fistulae likely to require surgery during the course of the study period, bowel surgery, other than appendectomy, within 12 weeks prior to screening visit and/or has planned surgery or deemed likely to need surgery for Crohn's disease during the study period, extensive colonic resection, subtotal or total colectomy, presence of ileostomies, colostomies or rectal pouches, fixed symptomatic stenoses of small bowel or colon, history of more than 3 small bowel resections or diagnosis of short bowel syndrome.
- Use of prohibited medications inside the specified washout period, and throughout the study. Prohibited medications include the following:
  - Use of any TNF alpha inhibitor, vedolizumab or natalizumab within 8 weeks
  - Use of glucocorticoids at doses greater than 10 mg prednisone orally QD, or an equivalent dose of other oral or parenteral glucocorticoids within 4 weeks
  - Use of cyclosporine, tacrolimus, sirolimus or mycophenolate mofetil within 4 weeks
  - Use of intravenous antibiotics for Crohn's disease within 4 weeks
  - Use of tube or enteral feeding, or elemental diet within 2 weeks
  - Rectal Treatment: Use of 5-aminosalicylates or corticosteroid enemas or suppositories within 2 weeks
  - Azathioprine, 6-mercaptopurine and methotrexate can be continued throughout the trial. These medications must have been used for >12 weeks, at stable dose for at least 3 weeks prior to screening
- Leukocytopheresis or granulocytopheresis within 2 weeks prior to screening
- Positive immunoassay for Clostridium difficile at screening
- History of unilateral or bilateral vagotomy, recurrent vaso-vagal syncope episodes, known obstructive sleep apnea, known history of cardiac rhythm disturbances, atrio-ventricular block of greater than first degree, or cardiac conduction pathway abnormalities other than isolated right bundle branch block or isolated left anterior fascicle block.
- Significant pharyngeal dysfunction or swallowing difficulties, pre-existing clinically significant vocal cord damage or hoarseness
- Previously implanted electrically active medical devices (e.g., cardiac pacemakers, automatic implantable cardioverter-defibrillators)
- Asthma or chronic obstructive pulmonary disease not controlled by medications, or any other disease causing clinically significant dyspnea at time of screening
- Active peptic ulcer disease

EFFICACY ENDPOINTS

PRIMARY ENDPOINT

- **Change in CDAI from baseline to Week 16 Visit**

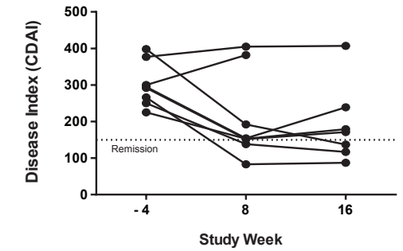
SECONDARY ENDPOINTS

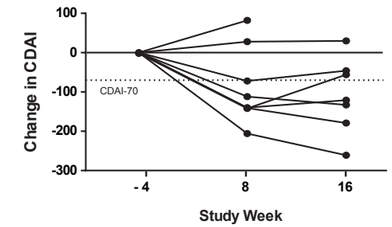
- **Rate of clinical response at Week 16 Visit defined as CDAI improvement from baseline of at least 70 points**
- **Rate of clinical remission at Week 16 Visit defined as CDAI less than or equal to 150**
- **Change in total SES-CD score from baseline to Week 16 Visit**

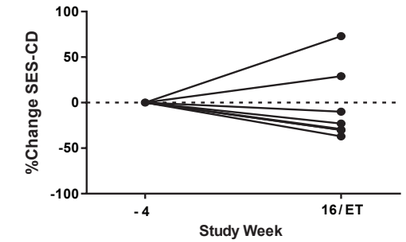
EXPLORATORY ENDPOINTS

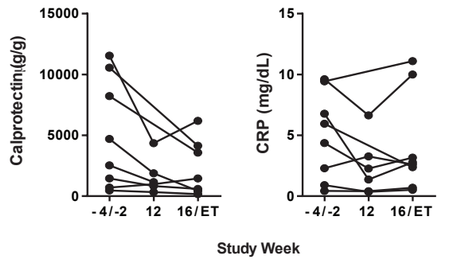
- **Fecal calprotectin levels**
- **hsCRP serum levels**
- **Whole blood LPS-induced in vitro TNF release assay**
- **Heart rate variability parameters**

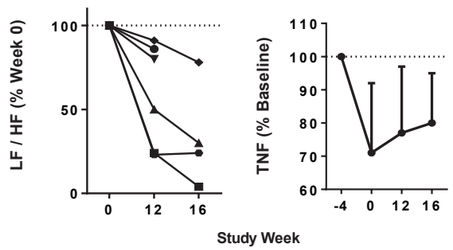
RESULTS











LF/ HF = Low Frequency/High Frequency (Heart Rate Variability); ET = Early Termination

CONCLUSIONS

- This interim report describes the experience of 8 patients with severe Crohn's, not responsive to TNF antagonists, with several patients also having failed other biologics.
- The CDAI scores were reduced by 70 points in 6 of 8
- CDAI remissions were achieved in 3 of 8
- SES-CDs were centrally read, and had showed reductions in 6 of 8
- hs-CRP and stool calprotectin levels were reduced in those had achieved clinical responses
- The HRV index of LF/HF ratio was reduced, consistent with increasing parasympathetic tone
- The TNF release was reduced with treatment, consistent with our experience in RA
- SAEs occurred in a number of patients. All but one was typical for severe Crohn's; one patient had a surgical infection.

IMPLICATIONS

- This study has shown VNS as an alternative treatment for Crohn's patients who have failed conventional treatments
- On the basis of these findings a larger controlled study should be performed

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Table 1.

Patient Demographics, History and Baseline Disease Severity	
Age (years)	38.8
Gender	5 / 8 Male
Race	6 / 8 Caucasian
Crohn's duration (years)	8.5
Prior Crohn's surgeries	
- Colonic resection	2 / 8
- Small bowel resection	1 / 8
- Fistula repair	3 / 8
- Abscess drainage	4 / 8
- Ileostomy (revised)	1 / 8
Prior Crohn's medications	
- TNF antagonists	8 / 8
- Vedolizumab	4 / 8
- Ustekinumab	2 / 8
- Corticosteroids	8 / 8
- Azathioprine	5 / 8
- Mercaptopurine	1 / 8
- Methotrexate	4 / 8
CDAI (mean, SD)	300 (60)
SES-CD (mean, SD)	22.3 (6.5)
Stool Calprotectin (µg/g, mean, SD)	5,024 (4,503)

Table 2.

Serious Adverse Events	Patient Number	Related to Implantation	Related to Device
Renal insufficiency and dehydration	0901-002	No	No
Dehydration	0901-002	No	No
Viral gastroenteritis	0901-001	No	No
Severe refractory Crohn's disease	0901-001	No	No
Ileus	0901-001	No	No
Worsening of Crohn's disease	2301-003	No	No
Pancolitis	0401-002	No	No
Postoperative surgical wound infection	2301-007*	Yes	No

*This patient had the device removed before receiving treatment