Pilot Study of the Safety and Efficacy of Neurostimulation of the Cholinergic Anti-Inflammatory Pathway Using an Active Implantable Vagal Nerve Stimulation Device in Patients With Rheumatoid Arthritis

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON35837

Source
ToetsingOnline

Brief title
SPM-005

Condition

- Autoimmune disorders

Synonym
painful swollen joints

Research involving

Human

Sponsors and support

Primary sponsor: Setpoint Medical
Source(s) of monetary or material Support: industry;setpoint

Intervention

Keyword: Arthritis, Device, Nerve, Stimulation

Outcome measures

Primary outcome

Primary Endpoint

* Change from Day 0 Visit to Day 42 Visit in DAS28

Secondary outcome

Secondary Endpoints

* Percentage of patients who achieve ACR 20, 50, and 70 at Day 42

* Percentage of patients who achieve EULAR response and EULAR remission

criteria at Day 42

* Change from Day 0 to Day 42 in EuroQoL EQ 5D instrument parameters

* Change from Day 0 Visit to Day 42 Visit in Whole Blood Assay Biomarker

LPS-inducible TNF release

* Change from Day 0 Visit to Day 42 Visit in Serum Biomarkers

* Change from Day 0 Visit to Day 42 Visit in Fluorescence-Activated Cell Sorter

(FACS) Panel Biomarkers

* Change from Day 0 Visit to Day 42 Visit in Synovial Biopsy cytokine and

mediator protein expression by immunohistochemistry

* Change from Day 0 to Day 42 in Synovial Biopsy cytokine gene expression by

quantitative PCR

Exploratory Endpoints

* Changes in DAS28, ACR 20, 50, and 70 response rate, Serum Biomarkers, FACS Panel Biomarkers, and Whole Blood Assay Biomarkers during treatment withdrawal between Day 42 Visit and Day 56 Visit

* Changes in DAS28, ACR 20, 50, and 70 response rate, Serum Biomarkers, FACS Panel Biomarkers, and Whole Blood Assay Biomarkers between Day 0 Visit and all visits other than Day 42

Safety Endpoints

The following Safety Endpoints will be assessed at all time points following enrollment at the Implantation Visit:

* Adverse Events

* Serious Adverse Events

* 12 Lead ECGs

* Vital Signs

* Safety Laboratory Studies

Study description

Background summary

Rheumatoid Arthritis (RA) is a devastating disease which affects approximately 1% of the population causing pain, and limiting physical activity and employment. RA leads to permanent physical deformity and disability from incompletely controlled inflammation and resultant structural damage to the

joints. In the last decade, the emergence of antagonists of tumor necrosis factor (TNF)-alpha and other biological response modifiers as treatments for RA has greatly improved the course and prognosis. Despite these advances, there remains a great medical need as current treatments have significant safety and cost disadvantages (McInnes, 2010).

The Cholinergic Anti-inflammatory Pathway (CAP) is an important physiological regulator of inflammation. A wealth of preclinical evidence suggests that activation of this pathway through electrical stimulation of the vagus nerve (VNS) can also be a feasible and effective means of reducing pathological systemic inflammation, and thus may represent a novel approach to treating RA and other human inflammatory diseases (Tracey, 2009; van Maanen, 2009a).

The aim of the current protocol is to begin to test this hypothesis in a pilot study in which RA patients will be surgically implanted with a commercially available vagal nerve stimulation device and the clinical safety and efficacy of neurostimulation of the cholinergic anti-inflammatory pathway (NCAP) will be assessed using standard clinical measures and surrogate biomarkers of RA.

Study objective

The primary efficacy objective is to determine the effect of NCAP on the clinical signs and symptoms of rheumatoid arthritis as assessed by the 28 Joint Disease Activity Score (DAS28).

The secondary efficacy objectives are to determine the effect of NCAP on:
* clinical signs and symptoms of rheumatoid arthritis as assessed by Americn College of Rheumatology (ACR) response criteria and European League Against Rheumatism (EULAR) response and remission criteria;
* health status and quality-of-life as assessed by the Euro-QoL EQ 5D instrument;
* biomarkers of inflammation as assessed by serum cytokine and mediator levels, changes in expression of circulating cell surface markers by FACS, and changes in LPS-inducible cytokine release in whole blood assays; and
* joint inflammation as assessed by changes in gene and protein expression of relevant inflammatory mediators in synovial biopsy tiss

The exploratory efficacy objectives are to:

* assess the clinical and biomarker response to a 14 day withdrawal of stimulation following 42 consecutive days of active treatment, and;

* assess the clinical and biomarker response at visits other than the Day 42 primary endpoint visit

The safety objectives are to determine the safety of NCAP as assessed by Adverse Events, Serious Adverse Events, 12 Lead ECG, Vital Signs, and Safety

Laboratory Studies

Study design

This will be an open-label multicenter study of the safety, efficacy and anti-inflammatory biological activity of NCAP using vagal nerve stimulation with a Cyberonics VNS implantable medical device.

Patients will sign informed consent and then will be screened, and if eligible will be enrolled in the study and admitted for surgical implantation of the device. After the implantation procedure and prior to hospital discharge the device will be set in inactive mode and the patient will recuperate from surgery for at least 14 days. The patients who consent to synovial biopsy will have the biopsy procedure done either at the time of device implantation, or a minimum of 4 days before the Day 0 Visit.
On Day 0, patients will visit the clinic, have baseline clinical assessments, safety laboratory studies, and biomarker studies performed, and will be given a single 60 second active stimulation at a frequency of 10Hz, with a 250 microsecond pulse duration, and an output current as maximally tolerated between a minimum of 0.25 mA to a maximum of 2.0 mA. Following the single 60 second stimulation on day 0, the time course of the biological response will be assessed with follow-up biomarker studies at several times thereafter. The patients will return on days 1 and 4 for biomarker assessments.
On day 7, the patient will return to clinic, will be given another in-clinic stimulation, and be instructed in the use of the device actuation magnet in order to self-administer treatments at home once daily thereafter. Attempts will be made at this and subsequent visits to increase the delivered output current to the maximally tolerated level. The patient will return to clinic on days 14, 21, and 28 for follow-up assessments. At the Day 28 Visit, if the patient has not achieved a moderate or good EULAR clinical response (i.e., a DAS28 level of 3.2 or better), the stimulation frequency will be increased from once daily to four times daily.
On day 42, all subjects will have their device inactivated, and will enter a 14 day treatment withdrawal period. On the Day 56 Visit, following clinical and biomarker assessments, the device will be reactivated and the treatment will be re-initiated at the same level and on the same schedule as the patient was receiving at the Day 42 Visit. This schedule will continue through the final study visit at day 84.

Intervention

Patients who meet any of the following criteria are not to be enrolled in this study:
* Inability to provide informed consent
* Significant psychiatric disease or substance abuse
* History of unilateral or bilateral vagotomy

* History of 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
* Intra-articular or parenteral corticosteroid treatment within 3 months of enrollment
* Any investigational small molecule drug within 30 days of enrollment, or any investigational monoclonal antibody or investigational soluble receptor within 3 months of enrollment

Study burden and risks

What are the general risks of participating in this research study?
Surgical placement of the device or stimulation of your vagus nerve with the device may cause all, some or none of the adverse events listed below.
The most common side effects reported in patients who had the device placed to treat their epilepsy or depression are symptoms of the throat including hoarseness, voice changes, throat pain, and swallowing difficulties, as well as shortness of breath, nausea, and indigestion. These symptoms happen almost only during the time the device is actually delivering electrical stimulation.

Other uncommon side effects reported include:
* slowing or other alterations of the heart rate,
* scarring or infections of the tissues around where the device is placed,
* worsening of certain lung and breathing diseases such as asthma, chronic obstructive pulmonary disease and sleep apnea in patients who already had these diseases when the device was placed.
* The device itself can move from where it was placed by the surgeon, and this might do damage to the vagus nerve, other nerves, blood vessels or other structures of the body.
* The device or any of its parts can break, in which case it may not deliver stimulation correctly.

Risks Relating to Surgical Placement of the Device
The surgical placement of the device (called *implantation*) can uncommonly cause damage to the vagus nerve, which typically improves with time, but in rare cases can be permanent. The most significant symptoms from damage to the vagus nerve are hoarseness or other voice, breathing or swallowing changes that

occur because some of nerves that go to the muscles of the throat come from the vagus. During the surgery for device placement other muscles, nerves, blood vessels or tissues in the area can also rarely be damaged. Infections occur uncommonly after placement of the device. These can usually be treated with antibiotics, but uncommonly they will require the device to be removed. In rare cases, when the device function is first being checked during the implantation surgery, significant slowing of the heart rate can occur. This will be closely monitored and treated should it happen.

Risks Relating toSurgical Removal of the Device
At the end of the study the device can be left in place and turned off so it does not deliver electrical stimulation. If you wish to participate in a longer term study, it can also be left on to continue to deliver stimulation. However, at any time during this study or the longer term study, you can decide to have it surgically removed. Uncommonly the device might also need to be removed if it becomes infected and the infection does not respond to antibiotics, or if the device malfunctions in a way that might be dangerous to you. The kinds of complications listed above for surgical implantation can also occur during removal. However, because some scarring around the components of the device usually happens over time, removal carries a higher risk of complications than implantation.

Chest X-ray
You will need to have a chest x-ray performed if you have not had one within the last 6 months. The amount of radiation received during a chest x-ray is about equivalent to 7-10 days of naturally occurring background radiation from sun, soil, food and water to which a person is exposed.

Blood Draws
You will need to have blood samples obtained throughout the study. The total amount of blood volume which will be taken during the course of the study is about 315 milliliters. Possible side effects of the blood draws are pain, bruising or bleeding at the site of needle puncture. Giving blood can occasionally cause headache, nausea or light-headedness.

Contacts

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Scientific

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Adult-onset rheumatoid arthritis of at least six months duration as defined by the 2010 ACR/EULAR classification criteria (Aletaha, 2010)
* Male or female patients, 18-75 years of age, inclusive
* Functional status I, II, or III as classified according to the ACR 1991 revised criteria (Hochberg, 1992)
* Patients must have active disease as defined by at least 4 active tender or swollen joints and CRP above 1.5 mg/dL, despite at least 3 months of treatment with methotrexate at a dose of up to 25 mg orally per week.
* Patients may have been previously treated with TNF antagonists, but must have failed by reason of inadequate safety, intolerance to side effects, or development of antibodies (i.e., secondary failures), and specifically must not have failed due to lack of efficacy (i.e., primary failures, defined as non-responders after at least 16 weeks of treatment). Such patients must have had a washout period of at least 6 weeks for etanercept, and at least 12 weeks for infliximab, adalimumab, golimumab, or certolizumab pegol prior to enrollment.
* At the discretion of the sponsor and the investigators, up to 2 of the patients enrolled may be patients who have failed both a TNF antagonist (either a primary or a secondary failure), AND have failed at least one other biological therapy having a non-TNF antagonist mechanism of action. Such patients may continue to use their current biologic therapy during the course of the study.
* Patients must have normal Screening Visit studies. Patients with abnormal but clinically insignificant Screening Visit studies may be included after discussion with and approval by the sponsor*s medical monitor.

* Women of childbearing potential must agree to use a double barrier method of contraception throughout the study

Exclusion criteria

* Inability to provide informed consent
* Significant psychiatric disease or substance abuse
* History of unilateral or bilateral vagotomy
* History of 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
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* 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
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Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-10-2011
Enrollment:	6
Type:	Actual

Medical products/devices used

Generic name:	Cyberonics VNS system
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO	
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL35732.018.11