Treatment of Complex Regional Pain Syndrome type 1: A randomized placebo controlled double-blind study with ARA 290, The CRPSARA Study

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Study AimsPrimary Aim: This is a proof-of-concept study to evaluate the effect of ARA 290 in pain of patients with CRPS1 by means of once daily subcutaneous injection with ARA 290 for 4 weeks. Secondary Aims: * Assess the predictive effect of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Peripheral neuropathies
Study type	Observational invasive

Summary

ID

NL-OMON37009

Source
ToetsingOnline

Brief title
Treatment of CRPS with ARA290

Condition

- Peripheral neuropathies

Synonym
nerve pain, neuropathic pain

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,Araim PharmaInc

Intervention

Keyword: CRPS, neuropathic pain, Pain, Treatment

Outcome measures

Primary outcome

The main study end-point is:

* Change in Numerical Rating Score of *pain now* as reported at the end of each treatment week and at the end of each week in the 4 weeks following treatment.

* Global Health self-assessment

Secondary outcome

Additional endpoints are:

* Change in Brief Pain Inventory

* Change in Short Form-36 questionnaire

* Change in Radboud Skills Questionnaire

* Change in the Walking Ability questionnaire

* Change in Hospital Anxiety and Depression Scale

* Change in Pain Coping Inventory

* Change in analgesic/antidepressant use

Study description

Background summary

Complex regional pain syndrome type 1 (CRPS1) is a chronic pain syndrome of the extremities. Most cases follow minor trauma or surgeries and symptoms persist

after healing appears complete. The patients suffer from severe and often chronic pain and disability. CRPS 1 is distinct from CRPS2; CRPS1 is a condition in which a nerve lesion cannot be identified, in CRPS2 it can. The cause of CRPS1 is currently under investigation. There is evidence of small fiber (A* and C-fibers) involvement. However, the similarities between the classical symptoms of inflammation and of CRPS have led to the suggestion that CRPS1 has an inflammatory origin. Neuroinflammation leads to a shift in the balance between nociceptive synaptic inhibition and excitation (by NMDA receptors) in the spinal dorsal horn causing central sensitization (ie. enhanced pain perception, allodynia and hyperalgesia). Previously we assessed the effect of long-term inhibition of the NMDA receptor on pain relief in CRPS1 patients (protocol P05.100, published in Pain 2009; 145: 304-311 [2]). The NMDA receptor (or N-methyl-D-aspartate receptor) is an excitatory glutamatergic receptor present in synaptic clefts of afferent pain pathways, especially in the spinal cord dorsal horn. Its long-term blockade (in protocol P05.100 patients received a 100-h ketamine infusion) results in long-term pain relief (up to 3 months) in CRPS1 patients.

In a recent set of animal studies we compared the effect of ketamine with ARA 290 in an animal model of chronic allodynia (a spared nerve injury model in which two branches of the sciatic nerve were cut). ARA 290 is an erythropoietin (EPO) analogue that activates the EPO-Receptor- *-common-receptor heterodimer complex and through this effect causes potent anti-inflammatory and tissue protective effects. ARA 290 does not activate the classical EPO receptor and consequently does not enhance hematopoiesis. ARA 290 produces pain relief in both animals and patients with chronic neuropathic pain (Protocol P10.131) when treatment is given on a regular basis (for example, every day). In the comparison between ketamine and ARA 290 in mice similar results were obtained, that is, prolonged pain relief upon regular administration of both agents. Furthermore, *-common-receptor knockout mice were insensitive to both ARA290 and ketamine. This later finding suggests a novel pathway of ketamine, ie through activation of the EPO *-common-receptor complex mediating chronic pain relief through an anti-inflammatory pathway, similar to ARA 290.

In the current study we will assess whether ARA 290 provides effective pain relief in the CRPS1 population with severe chronic pain. The major advantages of ARA 290 over ketamine are: (1) In contrast to ketamine, ARA 290 may be administered at home by the patients themselves; (2) In contrast to ketamine, ARA 290 is devoid of side effects.

The study will be performed in 40 CRPS1 patients using a placebo-controlled, randomized, double-blind design.

Study objective

Study Aims

Primary Aim:
This is a proof-of-concept study to evaluate the effect of ARA 290 in pain of patients with CRPS1 by means of once daily subcutaneous injection with ARA 290 for 4 weeks.

Secondary Aims:
* Assess the predictive effect of sensory tests as determined by quantitative sensory testing (QST, for example deep muscle pressure pain threshold) on the efficacy of treatment;
* Assess the effect of ARA 290 treatment on quality of life and overall mood-related parameters;
* Assess the effect of ARA 290 on daily functioning.

Study design

double blind, placebo controlled randomized

Study burden and risks

Little no side effects are expected

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion criteria will be the *Budapest Criteria* for CRPS1. These criteria have a high specificity and sensitivity for the diagnosis of the disease [1]. The criteria are:
(1) Continuing pain, which is disproportionate to any inciting event;
(2) Must report at least one symptom in three of the four following categories:
a. Sensory: reports of hyperesthesia and/or allodynia;
b. Vasomotor: reports of temperature asymmetry and/or skin color changes and/or color asymmetry;
c. Sudomotor/edema: reports of edema and/or sweating changes and sweating asymmetry;
d. Motor/trophic: reports of decreased motor ranges and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin);
(3) Must display at least one sign at time of evaluation in two or more of the following categories:
a. Sensory: hyperalgesia (to pinprick) and/or allodynia (to light touch and/or deep somatic pressure and/or joint movement);
b. Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or color asymmetry;
c. Sudomotor/edema: evidence of edema and/or sweating changes and sweating asymmetry;
d. Motor/trophic: evidence of decreased motor ranges and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin);
(4) There is no other diagnosis that better explains the signs and symptoms.
(5) Pharmacotherapy for CRPS symptoms (e.g., analgesics, antidepressants, and/or anticonvulsants) has been stable for at least 4 weeks

Exclusion criteria

Exclusion criteria are:
* Inability to give informed consent;
* Patients suffering from other pain syndromes;
* Clinically relevant abnormal history of physical and mental health, as determined by medical history taking and physical examinations obtained during the screening visit and/or prior to the administration of the initial dose of the study drug (as judged by the investigator);
* A semi recumbent systolic blood pressure of >160 mmHg and/or diastolic blood pressure of > 95 mmHg at screening;
* History of alcoholism or substance abuse within three years prior to screening;

* Positive pregnancy test or lactation
* Male subjects habitually using more than 21 units of alcohol per week and female subjects using more than 14 units of alcohol per week;
* Subject has a history of severe allergies, or has had an anaphylactic reaction or significant intolerability to prescription or non-prescription drugs or food;
* Subjects that received a vaccination or immunization within the last month;
* Participation in an investigational drug trial in the 3 months prior to administration of the initial dose of study drug or more than 4 times per year;
* Subject has undergone major surgery within three months prior to screening;
* Inability or unwillingness to self-administer ARA 290 via subcutaneous injections
* Any other condition that in the opinion of the investigator would complicate or compromise the study, or the well being of the subject

Study design

Design

Study phase:	2
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ARA 290
Generic name:	ARA 290

Ethics review

Approved WMO Date:	18-09-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-12-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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
EudraCT	EUCTR2012-003688-24-NL
CCMO	NL42051.058.12