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The use of anakinra in treating complex regional pain syndrome by blocking interleukin-1

Submission date
17/08/2021

Recruitment status
No longer recruiting

Registration date
01/09/2021

Overall study status
Completed

Last Edited
24/06/2025

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The aim of this study is to see if patients suffering from long-term complex regional pain syndrome can be helped with a drug called anakinra that suppresses part of the immune response that may contribute to this chronic painful condition.
Complex regional pain syndrome is a condition that results from trauma to an extremity that results in long-term pain that is disproportionate to the original injury and persists despite complete healing. It is a condition that is poorly responsive to treatments and often results in long-term physical disability and psychological distress.
We do not fully understand the reasons behind why complex regional pain syndrome occurs but laboratory studies suggest that these features are caused by abnormal activation in the immune system. One laboratory model of complex regional pain syndrome suggests that a specific component of the immune system plays a large contribution in perpetuating the ongoing pain and other abnormal physical features. In patients with complex regional pain syndrome, it is possible to take a sample of blood antibodies and administer these antibodies to mice. The mice then develop increased pain sensitivity when the antibodies are from patients with complex regional pain syndrome. This is highly suggestive that the immune system has an important contribution in how patients with complex regional pain syndrome have ongoing pain. In this model, a molecule called interleukin-1 which normally plays an important role in inflammation has a significant role in how the antibodies from patients with complex regional pain syndrome can increase pain and inflammation in mice.
Therefore, blocking interleukin-1 offers a potential way to treat patients with complex regional pain syndrome.
Anakinra is a drug in current medical use that blocks interleukin-1 activity and is used for medical conditions caused by abnormalities in the immune system. It has not been used in patients with complex regional pain syndrome. Blocking interleukin-1 by using anakinra may be useful in treating complex regional pain syndrome and the aim of this study is to administer it in 30 patients to check it is safe and well-tolerated before considering a larger trial to test for effectiveness.

Who can participate?
Adult patients with long-term complex regional pain syndrome for 18 months to 10 years that has been resistant to conventional treatment. No restrictions on the upper age range or gender. Participants will have to be willing to comply with study requirements such as attendance and filling out questionnaires. The risk to pregnancy is unknown so participants must be using precautions against getting pregnant if this is a possibility. There will be a list of criteria to judge whether patients are able to participate.

What does the study involve?
Participants will be asked to self-administer the drug once daily by injection into the fatty tissue under the skin for 4 months. They will be given pain diaries and be asked to attend six visits in total face-to-face to complete detailed questionnaires and measurements of limb volume and pain sensitivity tests. Blood samples will be taken to monitor for any adverse effects.

What are the possible benefits and risks of participating?
The benefit is that participants may get improvement in their medical condition and pain. The risk of anakinra is that it may suppress the immune system and increase the chance of getting infections. This risk is rare in the previous experience with this drug in rheumatological conditions and other minor side effects are pain at the injection site and headaches.

Where is the study run from?
The University of Liverpool (UK)

When is the study starting and how long is it expected to run for?
December 2020 to December 2024

Who is funding the study?
The Edelman Family Foundation (USA)

Who is the main contact?
1. Prof. Andreas Goebel, agoebel@liverpool.ac.uk
2. Mrs Dawn Greene, dgreene@liverpool.ac.uk / inca@liverpool.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-000052-19

Integrated Research Application System (IRAS)
288397

Protocol serial number
CPMS 49575, IRAS 288397

Study information

Scientific Title
Interleukin-1 receptor antagonist treatment for refractory complex regional pain syndrome

Acronym
INCA

Study objectives
Anakinra is safe and well-tolerated in patients with refractory complex regional pain syndrome.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 15/09/2021, Wales REC3 (Health and Care Research Wales Support and Delivery Centre, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)2920230457; Wales.REC3@wales.nhs.uk), REC ref: 21/WA/0184

Study design
Non-randomized study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Refractory complex regional pain syndrome

Interventions
The clinical trial involves identifying participants with long-term complex regional pain syndrome (CRPS) that has been unresponsive to the standard approved medical and non-medical therapies. The researchers believe that one of the reasons underlying CRPS is that of abnormalities in the immune system and in particular a molecule called Interleukin-1 that plays a role in the mechanisms of CRPS. Blocking Interleukin-1 can be achieved using a drug called anakinra that blocks the receptor that Interleukin-1 binds to. This will have the effect of reducing the effect of Interleukin-1 in CRPS. The trial involves administering an injection of anakinra which is a drug that blocks part of the immune system that may participate in the mechanism of how CRPS affects patients. This injection is injected under the skin and will be self-taught to participants to administer once a day for 120 days. The drug will be offered to all eligible participants and the aim is to determine safety and tolerability to plan a future randomised trial.

All consultations will take place in the pain management clinics at the Walton Centre, Liverpool and St Thomas Hospital London. Patients will be given diaries to fill in at home prior to their clinic visits. In addition, telephone consultations will be made after the face to face visits.

Information about the trial, detailing its purpose, design and risks/benefits will be offered to the participants prior to determining eligibility and consent.

Once eligibility and consent have been established, participants will undergo a baseline assessment, questionnaires and undergo a number of investigations such as blood tests and imaging if needed. These assessments aim to obtain data on the severity of symptoms, the impact on their physical and psychological function as well as measurements on the volume of the affected limb and a sensory profile of their painful area. Participants will then be taught how to administer the medication and given a supply to take home with the means to safely store sharp disposables. They will be taught how to fill in weekly and daily diaries to detail their pain scores and questionnaires on pain-related disability.

After the baseline visit, participants will undergo daily administration of anakinra by injection (self-administered at home) and the researchers will follow them up for four face to face visits at 30, 60, 90 and 120 days. A telephone call will be made 2 weeks after each face to face visit to review concomitant medication, adverse events and assess pain. The face to face visits will go

into detail about the effect and any adverse effect of the drug and participants will fill in detailed questionnaires about how pain has impacted their lives. In addition, there will be a detailed measurement of limb volume and sensory profile during these visits along with blood sampling.

At all times participants will be able to report adverse events and they will be given information on how to access the research team during working hours.

The trial drug is given only for 120 days and after the last face to face visit, participants will be asked to fill in weekly diaries and a final telephone follow-up made at the 180th day. This will mark the end of study participation.

Data will be collected to determine safety, tolerability and efficacy. This will allow a decision to be made to proceed to a randomised controlled trial in the future.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Anakinra

Primary outcome(s)
1. Safety of anakinra assessed using the number of patients without serious adverse events at baseline (0 days) – 180 days
2. Tolerance of anakinra assessed using the proportion of patients without serious adverse events at baseline (0 days) – 180 days
3. Persistent pain at injection site assessed using pain numerical rating scale (NRS) at baseline (0 days) - 180 days
4. CRPS-associated pain assessed using CRPS Severity Score at baseline (0 days) - 120 days

Key secondary outcome(s))
1. Registration rate assessed using monitoring report monthly throughout the study
2. Pain intensity assessed using CRPS Severity Score at baseline (0 days) - 120 days
3. Overall status assessed using Global Impression of Change (PGIC) at 120 days
4. Functional/psychological improvement assessed using Patient Health Questionnaire (PHQ-9), Brief Pain Inventory (BPI), Hospital Anxiety and Depression Scale (HADS) at baseline (0 days) - 120 days
5. Quality of life assessed using EQ5-5D-5L at baseline (0 days) - 180 days
6. Skin and limb sensitivity assessed using mechanical Quantitative Sensory Testing (QST) at baseline (0 days) - 120 days
7. Limb volume assessed by figure of 8 measurements at screening, baseline (0 days), 60 and 120 days
8. Work status (working, returned to work, etc) recorded at baseline (0 days) and 120 days

Completion date
13/12/2024

Eligibility

Key inclusion criteria

Current inclusion criteria as of 30/01/2024 (updated 13/02/2024):

1. A diagnosis of CRPS I or II according to the Budapest research criteria at the time of the assessment for this study
2. First documented diagnosis of Budapest CRPS by a healthcare professional not less than 18 months and not longer than 15 years before the screening assessment. A valid documented diagnosis must either include the term 'Budapest CRPS', or must include the term 'CRPS' and in addition documentation of the presence of signs and symptoms which allow making the Budapest diagnosis from the notes.
3. Pain intensity average 6 or greater on a 0-10-point numerical rating scale (NRS) over a minimum of seven consecutive daily entries prior to baseline (0 day) visit, with no single value below 5.
4. Completed a previous course of appropriate specialised physiotherapy
5. Poor response or intolerance to at least one anti-neuropathic pain medication such as tricyclic antidepressants or gabapentinoids.
6. If a woman of childbearing potential (WOCBP), to be willing to confirm the use of adequate birth control during the trial period unless pregnancy is impossible
7. Fertile male patients to be using contraception for the duration of therapy if sexually active with a female partner.
8. Age 18 years and over
9. Written and informed consent obtained from patient and agreement of patient to comply with the requirements of the study

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Previous inclusion criteria as of 07/03/2023:

1. A diagnosis of CRPS I or II according to the Budapest research criteria at the time of the assessment for this study
2. First documented diagnosis of Budapest CRPS by a healthcare professional not longer than 15 years before the screening assessment. A valid documented diagnosis must either include the term 'Budapest CRPS', or must include the term 'CRPS' and in addition documentation of the presence of signs and symptoms which allow making the Budapest diagnosis from the notes.
3. Pain intensity average 6 or greater on a 0-10-point numerical rating scale (NRS) over a minimum of seven consecutive daily entries prior to baseline (0 day) visit, with no single value below 5.
4. Completed a previous course of appropriate specialised physiotherapy
5. Poor response to anti-neuropathic pain medications- either unacceptable side effects or inadequate pain relief (Clinicians discretion)
6. If a woman of childbearing potential (WOCBP), to be willing to confirm the use of adequate birth control during the trial period unless pregnancy is impossible
7. Fertile male patients to be using contraception for the duration of therapy if sexually active with a female partner
8. Age 18 years and over
9. Written and informed consent obtained from patient and agreement of patient to comply with the requirements of the study.

Original inclusion criteria:

1. Diagnosis of complex regional pain syndrome I or II according to the Budapest research criteria
2. Disease duration of 18 months to 10 years
3. Average pain intensity of ≥6 on a 10-point numerical rating scale (NRS) over a minimum of 7 consecutive daily entries prior to baseline (0 day) visit, with no single value below
4. Completed a previous course of appropriate specialised physiotherapy
5. Poor response to anti-neuropathic pain medications- either unacceptable side effects or inadequate pain relief (Clinicians discretion)
6. If a woman of childbearing potential (WOCBP), to be willing to confirm the use of adequate birth control during the trial period unless pregnancy is impossible
7. Fertile male patients to be using contraception for the duration of therapy if sexually active with a female partner
8. Age 18 years and over

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
26

Key exclusion criteria
Current exclusion criteria as of 30/01/2024 (updated 13/02/2024):

1. Medical conditions that in the opinion of the study investigator would make it unsafe for participation or can adversely affect outcomes
2. Co-existing pain that in the view of the study doctor may make assessment of outcomes related to refractory moderate to severe CRPS unreliable
3. Ongoing relevant litigation where its conclusion is imminent during the course of the study
4. Medical Contraindications to anakinra such as moderate/severe or progressive renal impairment (CLCR <60 ml/min or eGFR <60 ml/min/1.73m2 or end stage renal disease, including dialysis), or hepatic impairment (defined as any value of transaminases, γ-glutamyl transpeptidase, or bilirubin greater than
2 times the upper normal limit) or hypersensitivity to anakinra or any of its excipients or to E.coli-derived proteins.
5. Previous use of anakinra
6. Current or recent (within 6 months) use of other immunosuppressants or biologics
7. Neutropenia defined as Absolute Neutrophil Count< 1.5 x 109/L
8. Requirement to receive a live vaccine during the trial duration.
9. Active or latent Tuberculosis infection

10. HIV, Hepatitis B or C carrier
11. Brittle asthma
12. Active malignancy or malignancy within 2 years
13. Ongoing alcohol or drug misuse at registration
14. Psychiatric or other mental health disorder which in the opinion of the study investigator may interfere with successful study participation
15. Commencing new therapy for refractory moderate to severe CRPS that may alter the outcome of the trial drug; this includes new pain
management program treatment. Equally patients who have completed a pain management program within the past 3 months
16. Subject is pregnant or breastfeeding, inadequate birth control, or the possibility of pregnancy during the study.
17. Patients who have a spinal cord or dorsal root ganglion stimulator whose average pain is less than 6 out of 10 when the stimulator is on.

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Previous exclusion criteria as of 07/03/2023:

1. Medical conditions that, in the opinion of the study investigator, would make it unsafe for participation or can adversely affect outcomes
2. Co-existing pain that, in the view of the study doctor, may make an assessment of outcomes related to refractory moderate to severe CRPS unreliable
3. Ongoing relevant litigation where its conclusion is imminent during the course of the study
4. Medical Contraindications to anakinra such as moderate/severe or progressive renal impairment (eGFR<60ml/min/1.73m²), hepatic impairment (defined as any value of transaminases, γ-glutamyl transpeptidase, or bilirubin greater than 2 times the upper normal limit) or hypersensitivity to anakinra or any of its excipients or to E.coli-derived proteins.
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6. Current or recent (within 6 months) use of other immunosuppressants or biologics
7. Neutropenia defined as Absolute Neutrophil Count <1.5 x 10e9/l
8. Requirement to receive a live vaccine during the trial duration
9. Active or latent tuberculosis infection
10. HIV, Hepatitis B or C carrier
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12. Active malignancy or malignancy within 2 years
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2. Co-existing pain that, in the view of the study doctor, may make an assessment of outcomes related to refractory moderate to severe CRPS unreliable
3. Ongoing relevant litigation where its conclusion is imminent during the course of the study
4. Medical contraindications to anakinra such as moderate/severe or progressive renal (eGFR <60 ml/min/1.73 m^2), hepatic impairment (defined as any value of transaminases, γ-glutamyl transpeptidase, or bilirubin greater than two times the upper normal limit) or hypersensitivity to anakinra or any of its excipients or to E. coli derived proteins
5. Previous use of anakinra
6. Current or recent (within 6 months) use of other immunosuppressants or biologics
7. Neutropenia defined as Absolute Neutrophil Count <1.5 x 10e9/l
8. Requirement to receive a live vaccine during the trial duration
9. Active or latent tuberculosis infection
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16. Subject is pregnant or breastfeeding, inadequate birth control, or the possibility of pregnancy during the study
17. Patients who have a spinal cord or dorsal root ganglion stimulator whose average pain is less than 6 out of 10 when the stimulator is on

Date of first enrolment
01/11/2021

Date of final enrolment
14/03/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St Thomas' Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
The Walton Centre
Lower Lane
Liverpool
United Kingdom
L9 7LJ

Sponsor information

Organisation
University of Liverpool

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Charity

Funder Name
Edelman Family Foundation

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from sponsor@liverpool.ac.uk.
Type of data: Full trial dataset
Whether consent from participants was obtained: Consent would be collected with specific statements: a. "I understand that relevant sections of my medical notes and any data collected during the study may be looked at by authorised individuals from the central study team and representatives of the Sponsor, regulatory authorities and the local NHS Trust. I give permission for these individuals to have access to my records and data." b. "I agree to allow information or results arising from this study to be used in future healthcare and/or medical research providing my confidentiality is maintained."

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results	version 1.0		24/06/2025	No	No
HRA research summary			28/06/2023	No	No
Protocol file	version 8.0	22/05/2024	24/06/2025	No	No
Statistical Analysis Plan	version 2.0	28/02/2024	24/06/2025	No	No