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An open-label study of the cerebrospinal fluid pharmacokinetics of intravenous Kineret® (recombinant methyionyl human interleukin-1 receptor antagonist [r-metHuIL-1RA]) in patients with subarachnoid haemorrhage

Submission date
22/06/2007

Recruitment status
No longer recruiting

Registration date
30/08/2007

Overall study status
Completed

Last Edited
21/08/2015

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
Subarachnoid haemorrhage (SAH) occurs when a blood vessel in the brain bursts and bleeds. It happens without warning and affects 6,000 patients every year in the UK. 13% of patients will die before reaching hospital. Of those who survive, blood flow to the brain may be reduced due to blood from the haemorrhage irritating the outer surface of brain arteries causing them to go into spasm and become narrower. Reduction in blood flow prevents oxygen reaching brain cells causing them to die. This is known as cerebral ischaemia and causes patients to experience symptoms similar to a stroke. However, these symptoms may not be immediately apparent as they commonly occur between 3-15 days after the initial haemorrhage. This is known as Delayed Cerebral Ischaemia. A protein called interleukin-1 (IL–1) is an important trigger for damage happening after cerebral ischaemia. After SAH, IL-1 causes the release of other proteins causing inflammation in the circulation and the brain. IL-1 can be blocked, limited or even reversed by another protein present naturally in our body - interleukin-1 receptor antagonist (IL-1Ra). A drug company has duplicated IL-1Ra and markets it as an anti-inflammatory treatment for rheumatoid arthritis (Kineret®). We have given this to a small number of patients after stroke and know that it is safe and we are now planning to move on to the next stage of developing the treatment. The aim of this study is to test if we are giving the right dose in the best way.

Who can participate?
Some SAH patients require insertion of an external ventricular drain (EVD) into the brain to remove excess cerebral spinal fluid (CSF). This is done as part of clinical care in order to relieve pressure within the brain but it also allows samples of CSF to be obtained. We aim to recruit SAH patients with an EVD within 72 hours of a SAH. Patients will be excluded if they are pregnant, have any existing serious infections, kidney problems or have received IL-1Ra before.

What does the study involve?
Five different doses of IL1Ra will be given to patients with five patients in each regime. Before, during and after the infusion, we will collect samples of blood and CSF to measure levels of IL-1Ra and other inflammatory proteins. We will also record everything that happens to the patients during participation. This data will be reviewed by an Independent Safety Committee at the end of each regime to ensure there are no safety concerns prior to dose escalation. At the end of the study, we hope to identify which dosing regimen best achieves concentrations in CSF that might prevent cerebral ischaemia. This will lead to further trials of IL-1Ra using this regime in order to measure its affect on levels of inflammation.

What are the possible benefits and risks of participating?
In patients who receive IL-1Ra for long periods of time, such as in rheumatoid arthritis, there is a slightly higher reported rate of infections and some patients have also been found to have made antibodies to IL-1Ra. This is not expected in this study, where it IL-1Ra is given over just four hours.

Where is the study run from?
Brain Injury Research Team, University of Manchester and Salford Royal NHS Foundation Trust, in collaboration with the Neurosurgical Team at Addenbrooke's Hospital, Cambridge

When is the study starting and how long is it expected to run for?
The study will start recruiting in September 2007 and will complete at the end of 2008.

Who is funding the study?
Medical Research Council (UK).

Who is the main contact?
Sharon Hulme
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Study website
http://www.hope-academic.org.uk/misah/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2007-002337-36

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Protocol version 3, 18/05/07; EudraCT: 2007-0023337-36

Study information

Scientific Title
Interleukin-1 receptor antagonist (IL-1RA) in subarachnoid haemorrhage (SAH) pharmacokinetic (PK) study 2

Study objectives
Infusion and bolus doses of intravenous Kineret® in patients with subarachnoid haemorrhage can achieve a rapid increase in the concentration of Kineret® in the cerebrospinal fluid, similar to that which has achieved neuroprotection in experimental studies.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Cambridgeshire 1 Research Ethics Committee, 23/08/2007, ref: 07/HO304/71

Study design
Phase I open-label descriptive pharmacokinetic study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Patient information can be found at: http://www.hope-academic.org.uk/misah/

Health condition(s) or problem(s) studied
Subarachnoid haemorrhage

Interventions
The study is an open-labelled study of Kineret® with five dose regimes. Initially, patients will be assigned to receive the lowest intravenous bolus dose regime of 100 mg plus a 4 mg/kg/h intravenous infusion for 4 hours (Regime 1). Once we have data on at least five patients and Cerebrospinal Fluid (CSF) and blood samples obtained at 30 minutes post-commencement of infusion, a further five patients will be entered into the study to receive Regime 2 (200 mg bolus plus a 2 mg/kg/h infusion for 4 hours). Preliminary pharmacokinetic modelling will occur after Regime 2 is complete. If this analysis shows that plasma and CSF concentrations in subarachnoid haemorrhage patients reflect those predicted and there are no safety concerns (see later section), the treatment assignment will be continued with three further regimes (Regime 3: 300 mg bolus, 2 mg/kg/h, Regime 4: 400 mg bolus, 6 mg/kg/h, Regime 5: 500 mg bolus, 10 mg/kg/h) in a step-wise fashion, each increasing the total dose given.

Intervention Type
Drug

Phase
Phase I

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

Primary outcome measure
CSF and plasma concentrations of Kineret® at 30 minutes post-commencement of infusion

Secondary outcome measures
1. Relationship between administered Kineret® and the central and peripheral Kineret® concentrations
2. Inflammatory biomarker concentrations
3. Adverse events

Overall study start date
01/11/2007

Completion date
01/10/2009

Eligibility

Key inclusion criteria
1. Patients with confirmed spontaneous subarachnoid haemorrhage who require the placement of an external ventricular drain
2. No other health problems that in the opinion of the Investigator would interfere with participation, administration of study treatment or assessment of outcomes
3. No confirmed or suspected serious infection
4. Renal function within normal limits
5. Aged 16 or above
6. Willing and able to give consent to take part or consent available from the patients representative
7. Likely to remain within the study centre for the next 7 days

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
100 patients recruited, 30 to receive intervention

Key exclusion criteria
1. Known allergy to E. coli or constituents of the investigational medicinal product
2. Previous or current treatment with Kineret® or anakinra
3. Previous participation in a clinical trial involving anakinra
4. Previous or current treatment potentially interacting with anakinra
5. Previous participants in other clinical intervention trials (within 30 days of last intervention)
6. Known to be pregnant or breastfeeding

Date of first enrolment
01/11/2007

Date of final enrolment
13/01/2009

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Hope Hospital
Salford
United Kingdom
M6 8HD

Sponsor information

Organisation
Salford Royal Foundation Hospital Trust (UK)

Sponsor details

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Sponsor type
Hospital/treatment centre

Website
http://www.hope-academic.org.uk/Academic/researchdevelopment/

ROR
https://ror.org/027rkpb34

Funder(s)

Funder type
Government

Funder Name
Medical Research Council (UK) (Grant ref: G0502030)

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2011		Yes	No