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Imaging immune cells in the human eye using Indocyanine-Green dye

Submission date	Recruitment status	[X] Prospectively registered
10/04/2017	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
12/04/2017	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
26/02/2020	Eye Diseases	

Plain English summary of protocol

Background and study aims
Indocyanine green (ICG) is a widely used dye employed since the 1960s for ocular angiography, where a dye is injected into a vein in the arm, which flows through the blood to the blood vessels in your eye so that photographs can be taken of the back of the eye. It is used daily within the NHS for the diagnosis and monitoring of many eye diseases including age-related macular degeneration, uveitis and ocular tumours. It is approved and safe with only occasional side effects of nausea and rash, and severe allergy (anaphylaxis) is rare (0.05%). It is not currently possible to reliably see and track immune cells in living human tissues. The eye is unique as the only readily accessible and transparent organ in the human body. ICG injected into mice can label immune cells, which can then be seen in the eye using the same commercially available imaging equipment used for humans. Particular immune cells called macrophages accumulate ICG dye to become bright enough to be seen when imaging the eye, but this typically took up to 48 hours. No other studies have looked at whether ICG can label cells in this way before and so to advance this work towards use in humans, a study is required. Building on the animal studies, this is the first study to look at immune cells in the eyes of humans after administration of ICG. Currently ICG is already used as part of current standard of care for a wide range of eye diseases, but images of the eye are only taken for up to 30 minutes. This means that any labelling of cells will not have been seen before, as it is unlikely that any cells will have had enough time to be labelled with the ICG within 30 minutes.

Who can participate?
Patients aged 18 or over who are receiving ICG as part of standard care for eye diseases, who have eye diseases where ICG is not normally used, and healthy volunteers with no eye disease

What does the study involve?
Participants receive ICG injected into a vein and have eye images taken beyond the current 30 minutes, to see if the cells become visible with time. Participants undergo repeated photographs of the back of the eye at 2, 4, 6, 8, 24, 48 hours and 7 days after the ICG dye has been injected. If cells are seen blood tests are carried out to determine if the cells can also be seen circulating in the blood and confirm that they are immune cells.

What are the possible benefits and risks of participating?
No direct benefits to the participants are expected from this study, but their contribution will advance research which may lead to improved methods for diagnosing and monitoring eye diseases in the future. For those not receiving the ICG dye as part of normal care by their eye doctor, there is a small additional risk from the dye, which can include side effects of rash, nausea, itching and rarely a severe allergic reaction (anaphylaxis). Participants' pupils are dilated with drops which can blur the vision for several hours.

Where is the study run from?
University Hospitals Bristol NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January to December 2017

Who is funding the study?
David Telling Charitable Trust (UK)

Who is the main contact?
1. Dr Colin Chu (scientific)
2. Ms Monalisa Bora (public)
monalisa.bora@uhbristol.nhs.uk

Contact information

Type(s)
Scientific

Contact name
Dr Colin Chu

ORCID ID
https://orcid.org/0000-0003-2088-8310

Contact details
University of Bristol
F38, Biomedical Sciences Building
University Walk
Bristol
United Kingdom
BS8 1TD

Type(s)
Public

Contact name
Ms Monalisa Bora

Contact details
Clinical Research Unit
Bristol Eye Hospital
Lower Maudlin Street

Bristol
United Kingdom
BS1 2LX
+44 (0)117 342 4770
monalisa.bora@uhbristol.nhs.uk

Additional identifiers

Integrated Research Application System (IRAS)
217189

Protocol serial number
Ref: 2714

Study information

Scientific Title
Prospective clinical study of Indocyanine-Green dye immune cell imaging in the human eye

Acronym
ICI Study

Study objectives
The aim of this study is to evaluate the feasibility of using intravenous ICG dye to image immune cells within the eyes of patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South West - Frenchay REC, 16/03/2017, ref: 17/SW/0030

Primary study design
Interventional

Study design
Single-centre unmasked interventional study

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Known ocular diseases including neovascular age-related macular degeneration, posterior uveitis and central serous retinopathy

Interventions
The first 12 patients will undergo ICG angiography as already clinically required by their treating physician. Additional retinal imaging will be performed at 2, 4, 6, 8, 24, 48 hours and 7 days. Two

blood tests will be taken during this period. Subsequently, three healthy volunteers and three patients without clinical indication for ICG angiography will undergo injection with ICG and be followed in an identical fashion.

Intervention Type
Mixed

Primary outcome(s)
Visualisation of ICG cell labelling in the eyes of patients with diseases affecting the eye, based upon retinal photograph images assessed by the chief investigator from any session up to the 7 days

Key secondary outcome(s)
1. The optimum time after ICG injection for cells to be seen
2. Absence of ICG cell signals in control eyes without disease
3. Detection and characterisation of ICG labelled cells using flow cytometry in peripheral blood samples taken following ICG injection

Completion date
01/12/2017

Eligibility

Key inclusion criteria
1. 18 years of age or over with legal capacity to consent
2. Able to travel and attend the full programme within the funded travel cost budget

In addition, ocular inclusion criteria must be met:

Cohort 1 - recruitment of 8 patients:
1. With likely or suspected Choroidal Neovascular Membrane or Central Serous Retinopathy that clinically requires ICG angiography (with or without combined fluorescein angiography)
2. Macular sub-retinal fluid is present and at least 500µm in diameter on a spectral-domain OCT scan
3. Any obscuring haemorrhage should not exceed more than 50% of the area of the sub-retinal fluid
4. Not due for intravitreal injection or photodynamic therapy within the first 48 hours of the study period

Cohort 2 - recruitment of 4 patients:
1. With likely or suspected posterior uveitis or panuveitis that clinically requires ICG angiography (with or without combined fluorescein angiography)
2. Clinically suspected vasculitis
3. No intravitreal therapy has been administered within 3 months prior or will be administered during the study period
4. Mild vitritis only (with a SUN Haze score ≤2)

Cohort 3 - recruitment of 3 healthy control volunteers:
1. No known ocular pathology
2. No known refractive error larger than +3.00 dioptres or -3.00 dioptres spherical equivalent in either eye

3. Self reported normal community optometry examination within one year prior to recruitment
4. Normal colour fundal photography at start of study

Cohort 4 - recruitment of 3 patients:
1. Known ocular pathology where ICG angiography is not normally indicated
2. Diagnoses can include Diabetic Macular Oedema, Proliferative Diabetic Retinopathy, cystoid macular oedema, geographic atrophy or other forms of uveitis not included in Cohort 2
3. Patients meeting the criteria for Cohorts 1 and 2 may also be included, but given ICG alone without combined Fluorescein as in the usual standard of care

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
12

Key exclusion criteria
1. Known fluorescein, ICG, iodine or shellfish allergy
2. Any known contraindication to topical Tropicamide and Phenylephrine dilating drops
3. Known renal (eGFR ≤80 mL/min/1.73m2) or hepatic dysfunction or active disease that in the opinion of the investigator will contraindicate the administration of ICG
4. Unable to be easily imaged on Spectralis, Optos or Topcon retinal imaging machines (e.g. marked kyphosis or physical impairment)
5. Significant media opacity leading to poor image quality. (e.g. vitreous haemorrhage or cataract)
6. Unable to donate a peripheral blood sample or known HIV, Hep B or C
7. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until the termination of gestation. A pregnancy test will be performed on all female participants of childbearing age prior to ICG injection
8. Each participant may only enter the study once and cannot currently be enrolled in another research trial

Date of first enrolment
08/05/2017

Date of final enrolment
08/11/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University Hospitals Bristol NHS Foundation Trust
Bristol Eye Hospital
Lower Maudlin Street
Bristol
United Kingdom
BS1 2LX

Sponsor information

Organisation
University of Bristol

ROR
https://ror.org/0524sp257

Funder(s)

Funder type
Charity

Funder Name
David Telling Charitable Trust

Results and Publications

Individual participant data (IPD) sharing plan
The qualitative retinal images will be stored for up to 5 years in the clinical research unit of Bristol Eye Hospital. Given the amount and size of photographic material and lack of designated repositories, it is not practicable to make this widely available, however reasonable requests can be accommodated on an informal basis at the discretion of the chief investigator.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	13/02/2020	24/02/2020	Yes	No
HRA research summary			28/06/2023	No	No