ISRCTN32207582 https://doi.org/10.1186/ISRCTN32207582

Clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy

Submission date 10/07/2014	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 10/07/2014	**Overall study status** Completed	
Last Edited 12/03/2021	**Condition category** Eye Diseases	

Plain English summary of protocol

Background and study aims
Diabetes can affect many parts of the body, including the eye where it typically affects the light-sensing tissue, the retina. This is called diabetic retinopathy and in its most severe form, proliferative diabetic retinopathy (PDR) can cause severe visual loss due to bleeding and scarring of the retina from the abnormal growth of new blood vessels. This condition is the most common cause of severe visual loss in the working age group, and the rate of visual impairment in the elderly due to diabetic retinopathy is also increasing. The current treatment for PDR is multiple laser shots to the peripheral retina, which causes new blood vessels to regress. However, this is unsuccessful in 40-50% of cases, and further loss of vision may occur. This study aims to explore a new method of causing new blood vessel regression in PDR by repeated injections into the eye of a new drug, aflibercept. Such drugs work by preventing the action of vascular endothelial growth factor (VEGF), a small molecule made by the retina in response to normal retinal blood vessels being blocked off by diabetes. Unchecked, VEGF causes the growth of new blood vessels, which are an attempt by the body to repair or replace the old blocked vessels. However, the new blood vessels are abnormal and have a high risk of bleeding. To date, small studies in a few patients have shown promising short-term results for anti-VEGF agents in PDR. This study aims to explore the effectiveness of afilbercept compared to laser therapy in PDR.

Who can participate?
Adult patients with diabetes mellitus who also have PDR can take part in this study.

What does the study involve?
Patients are randomly allocated either to treatment with repeated eye injections of aflibercept about every 4-12 weeks or to the usual laser treatment which will be repeated as necessary throughout the study according to existing treatment guidelines. The outcome of the treatments will be compared at 12 months and will include various tests including treatment satisfaction and quality of life questionnaires. In addition, 40 participants will undergo a further 1 hour of retinal photography and image analysis at the start of the study and after 12 and 52 weeks to explore the effect of this drug on the retina and new blood vessels. Each patient will be followed up for 12 months.

What are the possible benefits and risks of participating?
The benefit is the opportunity to receive a new treatment option for PDR. Currently, this condition is treated with laser that destroys areas of the retina. Unlike laser treatment, the new treatment is a course of injections into the eye. There will be a pricking sensation during the procedure but the study eye will be prepared with numbing medication before the procedure to make the patient comfortable. We believe that this new treatment option does not cause the known side effects of laser treatment which include a tendency to lose peripheral field of vision with repeated laser, decreased colour and contrast, and difficulties with night vision. The new treatment of repeated injections may cause an infection in the eye, which may be sight threatening, but this is a rare complication with a frequency of 1 in every 1000 injections.

Where is the study run from?
The study will take place in about 17 ophthalmology centres in the UK.

When is the study starting and how long is it expected to run for?
August 2014 to December 2015.

Who is funding the study?
National Institute for Health Research (NIHR) (UK).

Who is the main contact?
Dr Sobha Sivaprasad
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2013-003272-12

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
16922

Study information

Scientific Title
Clinical efficacy and mechanistic evaluation of aflibercept for proliferative diabetic retinopathy: a multicentre Phase IIb randomised active-controlled clinical trial

Acronym
CLARITY Version 1.0

Study objectives
To evaluate whether best corrected visual acuity following intravitreal aflibercept therapy is non-inferior to panretinal photocoagulation (PRP) in eyes with proliferative diabetic retinopathy (PDR) at 52 weeks as measured by ETDRS letters.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London - South East; 14/LO/0203

Study design
Randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Topic: Diabetes, Ophthalmology; Subtopic: Both, Eye (all Subtopics); Disease: Ophthalmology, Other

Interventions
220 patients with treatment naive or post PRP active retinal neovascularisation in at least one eye will be randomised 1:1 to intravitreal aflibercept versus PRP for a period of 52 weeks.

Intervention Type
Mixed

Primary outcome measure
To evaluate whether best corrected visual acuity following intravitreal aflibercept therapy is non-inferior to panretinal photocoagulation (PRP) in eyes with proliferative diabetic retinopathy (PDR) at 52 weeks as measured by ETDRS letters

Secondary outcome measures
1. To measure the effect of intravitreal aflibercept therapy, relative to panretinal photocoagulation on additional visual functions and quality of life outcomes including:
1.1. Unilateral and binocular Estermann visual fields defects
1.2. Binocular visual acuity and low luminance visual acuity
1.3. Visual acuity outcomes in terms of visual gain or loss
1.4. Contrast sensitivity using Pelli Robson charts
1.5. Vision-related quality of life measured by VFQ-25 and RetDQoL
1.6. Diabetic retinopathy treatment satisfaction outcomes (RetTSQ)
1.7. Generic health-related quality of life using the EQ-5D, ICECAP-A, and CSRI.
2. To estimate incremental cost-effectiveness of intravitreal aflibercept versus standard PRP treatment at 52 weeks
3. To determine the proportions of treatment-naïve and post-treatment PRP eyes in both arms that do not require panretinal photocoagulation through 52 weeks after basic treatment of three loading doses of aflibercept or initial completion of PRP
4. To compare between arms the regression pattern at 12 weeks and the regression and reactivation patterns of retinal neovascularisation at 52 weeks
5. To compare the proportion of patients with one-step and three-step improvement or worsening of diabetic retinopathy between treatment arms at 12 and 52 weeks as per schedule of assessment
6. To explore the difference in safety profile between intravitreal aflibercept and panretinal photocoagulation at 52 weeks, in terms of proportion of patients developing macular oedema (defined as central subfield thickness of >300 µm on SD-OCT due to clinical evidence of macular oedema), any de novo or increase in existing vitreous haemorrhage, de novo or increasing tractional retinal detachment, neovascular glaucoma, and requirement for vitrectomy. The indication for vitrectomy will be reported

Overall study start date
15/08/2014

Completion date
01/12/2015

Eligibility

Key inclusion criteria
1. Subjects of either sex aged 18 years or over
2. Diagnosis of diabetes mellitus (type 1 or type 2)
3. Best corrected visual acuity in the study eye better than or equal to 54 ETDRS letters (Snellen visual acuity 6/18)
4. PDR with no evidence of previous PRP or presence of new or persistent retinal neovascularisation despite prior PRP that (a) requires treatment in the opinion of the investigator and (b) there is sufficient space in the peripheral retina to perform more PRP

treatment. In patients with both eye involvement, the eye with no PRP or the least number of PRP burns will be randomised as the study eye. If both eyes have had no PRP before, the eye with the better visual acuity will be randomised as the study eye
5. Media clarity, pupillary dilation and subject cooperation sufficient for adequate fundus photographs. Eyes with mild pre-retinal haemorrhage or mild vitreous haemorrhage that does not interfere with clear visualisation of the macula and optic disc are eligible for this study
6. Ability to give informed consent
7. Women should use effective contraception, be postmenopausal for at least 12 months prior to trial entry, or be surgically sterile

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 220; UK Sample Size: 220; Description: 220 patients with 110 in each arm. SS allows for 17% drop out rate in follow-up

Key exclusion criteria
The following exclusions apply to the study eye only (i.e. they may be present for the non-study eye):
1. Coexistent ocular disease that will affect visual outcome
2. Moderate or dense vitreous haemorrhage that prevents clear visualisation of the macula and /or optic disc or prevents PRP treatment
3. Significant fibrovascular proliferation or tractional retinal detachment in the posterior pole
4. Prior vitrectomy
5. Presence of macular oedema at baseline confirmed by SDOCT as central subfield thickness of more than 300 µm due to the presence of morphological evidence of diffuse or cystoid oedema. Please see rescreening of patients
6. Other causes of retinal neovascularisation
7. Iris or angle neovascularisation and neovascular glaucoma
8. Anticipated need for cataract extraction or vitrectomy within the next 12 months
9. Known allergy to fluorescein or any components of aflibercept formulation
10. Previous intravitreal anti-VEGF or steroid treatment for diabetic macular oedema in the last 4 months
11. Panretinal photocoagulation within the last 8 weeks
12. Aphakia
13. Uncontrolled glaucoma as per investigator's judgement
14. Severe external ocular infection
15. The participant should not have an HbA1C level of more than 12%.
16.The participant should not have a blood pressure of more than 170/110 mmHg
17. A medical condition that, in the opinion of the investigator, would be preclude participation in the study

18. Myocardial infarction, stroke, transient ischaemic attack, acute congestive cardiac failure or any acute coronary event within 6 months of randomisation
19. Dialysis or renal transplant
20. Pregnant women
21. Women of childbearing potential who do not agree to use effective potential contraception during the study and for at least 3 months after the study has finished. Effective contraception is defined as one of the following:
21.1. Barrier method: condoms or occlusive cap with spermicides
21.2. True abstinence: when it is in line with the preferred and usual lifestyle of subject. Periodic abstinence (e .g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
21.3. Female contraception: have had tubal ligation or bilateral oophorectomy (with or without hysterectomy)
21.4. Male partner sterilisation. The vasectomised male should be the only partner for the female participant.
21.5. Use of established oral, injected or implanted hormonal methods of contraception and intrauterine device.
22. Breastfeeding women
23. Males who do not agree to use an effective form of contraception for the duration of the study and 3 months after the study has finished. Effective contraception is defined as one of the following:
23.1. Barrier method: condoms or occlusive cap with spermicides.
23.2. True abstinence: when in line with preferred and usual lifestyle of the subject. Periodic abstinence and withdrawl are not acceptable methods of contraception
23.3. Male sterilisation (vasectomy)
23.4. Female partners using contraception
24. Participation in an investigational trial involving an investigational medicinal product within 30 days of randomisation

Date of first enrolment
15/08/2014

Date of final enrolment
01/12/2015

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
King's College London
London
United Kingdom
SE1 3QD

Sponsor information

Organisation
Moorfields Eye Hospital NHS Foundation Trust (UK)

Sponsor details
162 City Road
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/03zaddr67

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Coordinating Centre (UK); Grant Code: 12/66/15

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?
Protocol article	protocol	14/09/2015		Yes	No

Results article	results	03/06/2017		Yes	No
Results article	results	11/03/2021	12/03/2021	Yes	No
HRA research summary			28/06/2023	No	No