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Using panitumumab with ranibizumab injected into the eye to treat exudative age-related macular degeneration

Submission date
30/10/2023

Recruitment status
Recruiting

Registration date
20/12/2023

Overall study status
Ongoing

Last Edited
27/12/2023

Condition category
Eye Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Exudative maculopathies, like neovascular age-related macular degeneration (AMD) or polypoidal choroidal vasculopathy, involve the growth of problematic new blood vessels under the retina. This can lead to vision issues in the central part of the eye.

Doctors now use special injections containing anti-VEGF antibodies (like ranibizumab and others) to treat these conditions. These injections have dramatically improved the outcomes for patients by reducing these new blood vessels. This also helps reduce fluid buildup in the eye, which can improve central vision.

In these conditions, the new blood vessels also cause changes in a layer called the retinal pigment epithelium (RPE). These changes prevent the RPE from doing its job properly, which affects the photoreceptor cells responsible for vision.

Although the treatment helps with the new blood vessels, it can't fix the issues caused by these changes in the RPE. Scientists have looked into a molecule called epidermal growth factor (EGF) as it seems to encourage the growth of these RPE cells. Blocking EGF can help slow down the problem.

Some studies have shown that people with these eye conditions have high levels of EGF. This has led to the idea of using EGF receptor (EGFR) antibodies alongside VEGF antibodies to reduce these issues further.

Who can participate?
The people we want to include in our study must be at least 55 years old. They should have okay eyesight, with the ability to see clearly within a certain range on an eye chart. Also, they should have a specific eye condition related to age-related macular degeneration (AMD), where there are abnormal blood vessels in a specific part of the eye. Their retinas need to be a certain

thickness, and their eye pressure should be normal. Additionally, their eye should be clear, without any other major eye problems, except maybe for cataracts or artificial lenses. They shouldn't have had certain types of eye surgery before.

If someone can't make it to our check-up appointments or doesn't really understand what we're trying to do in this study, we won't include them.

What does the study involve?
We used a method where sealed envelopes were involved to randomly divide the patients into three groups in equal numbers. In the "high-dose study group," patients received injections directly into their eyes: one with ranibizumab (Lucentis®, from Genentech Co., South San Francisco, CA, USA) at a dose of 0.5 mg, and another with panitumumab (Vectibix®, from Amgen Co, Thousand Oaks, CA, USA) at a dose of 1.8 mg. In the "low-dose study group," patients got similar eye injections, but with a slightly lower dose of panitumumab, 1.2 mg. The control group only received injections of ranibizumab at a dose of 0.5 mg directly into their eyes. These injections happened every two months for two years.

What are the possible benefits and risks of participating?
Better visual outcome; risks of intraocular infections, risk of intraocular toxicity by the drugs

Where is the study run from?
Ufa Eye Research Institute (Russia)

When is the study starting and how long is it expected to run for?
December 2022 to December 2026

Who is funding the study?
Ufa Eye Research Institute (Russia)

Who is the main contact?
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Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Intravitreal panitumumab combined with intravitreal ranibizumab for exudative age-related macular degeneration

Acronym
Panitumumab-AMD-Study

Study objectives
Subretinal fibrosis in exudative macular diseases such as exudative age-related macular degeneration consists of prolifereated retinal pigment epithelium (RPE) cells. RPE cells have epidermal growth factor (EGF) receptors, and in cell culture, RPE cell migration and proliferation is reduced by application of EGF receptor blockers. We hypothesize, that addition of panitumumab as an EGF receptor blocker reduces the subretinal fibrotic scar formation in eyes with exudative, neovascular age-related macular degeneration

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 07/12/2022, Ethics Committee of the Academic Council of the Ufa Eye Research Institute (90 Pushkin Street, Ufa, 450008, Russian Federation; +7(347)272-37-75; eye@bashgmu.ru), ref: Reference number not provided

Study design
Randomized controlled interventional trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Exudative age-related macular degeneration

Interventions
This is a 2-year, prospective, randomized, double-masked, controlled study of the safety and efficacy of repeated intravitreal injections of panitumumab combined with intravitreal injections of ranibizumab among patients with choroidal neovascularization associated with AMD. We perform a prespecified primary efficacy analysis at 12 months. The primary efficacy end point is

the proportion of patients who had lost fewer than 15 letters (approximately 3 lines) from baseline best corrected visual acuity, as assessed with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, with the use of standardized refractometry and a testing protocol at a starting test distance of 2 m. The Ethics Committee of the Academic Council of the Ufa Eye Research Institute approved the study and informed written consent was obtained from all participants (dated: 7.12.2022). The eligibility of lesions is confirmed by a reading center with the use of standardized criteria and trained graders who are unaware of patients' treatment assignments. Patients provide written informed consent before determination of their full eligibility. The screening process can take up to two weeks.

The intravitreal injections are carried out in the operation theater under sterile conditions in topical anesthesia. In a first step, a paracentesis is performed to release about 0.1 to 0.2 mL of aqueous humor to reduce the intraocular volume and to create space for the following intravitreal injection of panitumumab and/or ranibizumab. A paracentesis performed prior to an intravitreal injection has been shown to be a safe procedure and can prevent intraocular pressure (IOP) spikes after injections. The sampled aqueous humor samples are collected and deeply frozen for later biochemical analyses. The intravitreal injection is performed transconjunctivally in the temporal inferior quadrant in a distance of 3.0 to 3.5 mm from the limbus. Care is taken that before the injection, the conjunctiva was slightly shifted so that the conjunctival perforation site was not identical with the scleral perforation site. The injections in volumes of 50 µL (0.5 mg ranibizumab), 120 µL (1.2 mg panitumumab) and 180 µL (1.8 mg panitumumab) are directed into the center of the vitreous cavity. Depending on the IOP at the end of the injection and of the alignment of the scleral perforation site, some fluid from the vitreous cavity may spill back under the conjunctiva. Testing of the visibility of hand movements follows the intravitreal injections. An ointment containing a topical antibiotic and a topical steroid (levofloxacini 0.5%, Lekko, Russia dexamethasone 0.1%. «Belmedpreparaty», Republic of Belarus) is applied.

Dose considerations:
In animal studies, a dose of 20 µg EGFR antibody (molecular weight: 175 kDa; #2232, Cell Signaling Technology, Danvers, MA, USA) was used in guinea pig eyes with a diameter of about 8 mm, corresponding to an ocular volume of about 268 mm3.32-35 It related to an intraocular concentration 0.07 µg EGFR antibody / mm3). It corresponded to a dose of 0.72 mg EGFR antibody in a highly myopic adult human eyes with an axial length of 27 mm or an intraocular volume of approximately 10.306 mm3, assuming a spherical eye shape. Taking into account the molecular weight of panitumumab (144.3 kDa) compared to the molecular weight of the antibody used in the guinea pig study (175 kDa), the equimolar dose of panitumumab is 0.59 mg. This dose of 0.6 mg panitumumab is approximately 1/700 of the systemically applied dose of panitumumab (Vectibix®) administered intravenously every two weeks for oncological indications according to the SmPC (summary of product characteristics) (6 mg panitumumab / kg body weight or about 420 mg panitumumab for a patient with a body weight of 70 kg).36 Panitumumab (Vectibix®) is delivered by the pharmaceutical company in a concentration of 100 mg/5 mL (or 20 mg/mL) and has to be diluted to a concentration of 10 mg/mL. The doses of 1.2 mg and 1.8 mg panitumumab for intravitreal application thus led to an injection volume of 120 µL and 180 µL, respectively.
Based on the experiences gathered worldwide with the intravitreal application of bevacizumab (Avastin®) used for the treatment of neovascular macular degeneration and other retinal diseases, an intravitreally injected dose of 1.25 mg bevacizumab (molecular weight: 149 kDa), corresponding to a molecular dose of 0.000,000,008 mol bevacizumab, is intraocularly and systemically well tolerated. In a similar manner, the intravitreal application of ranibizumab (Lucentis®) (also for the therapy of exudative macular degeneration) in a dose of 0.50 mg ranibizumab (molecular weight: 48 kDa) (corresponding to a molecular dose of 0.000,000,01 mol

ranibizumab) is intraocularly and systemically well tolerated. A dose of 1.8 mg panitumumab corresponds to 0.000,000,013 mol panitumumab, which is about 1.3 fold of the molar dose of ranibizumab. In oncology, Avastin® (bevacizumab) is given intravenously every three weeks at a dose of 15 mg / kg body weight (or 1.2 g bevacizumab at a body weight of 80 kg). The routinely and intravitreally applied dose of bevacizumab of 1.25 mg is thus about 1/1,000 of the intravenously applied dose of bevacizumab in oncology. A roughly similar ratio is obtained when the systemically routinely applied dose of 420 mg panitumumab is compared with an intravitreally applied dose of 1.2 mg or 1.8 mg panitumumab.

Randomization and Examinations
Using the sealed envelope technique, the patients are randomly assigned in a 1:1:1 ratio into three groups. The eyes in the “high-dose study group” receive intravitreal injections of ranibizumab (Lucentis®, Genentech Co., South San Francisco, CA, USA) at a dose of 0.5 mg combined with an intravitreal injection of panitumumab (Vectibix®, Amgen Co, Thousand Oaks, CA, USA) at a dose of 1.8 mg; the eyes of the “low-dose study group” receive intravitreal injections of ranibizumab at a dose of 0.5 mg combined with an intravitreal injection of panitumumab at a dose of 1.2 mg; and the eyes of the control group only receive intravitreal injections of ranibizumab at a dose of 0.5 mg. The injections were given in two-monthly intervals for two years.
The evaluating physician is unaware of the patient's treatment assignment; the physician who administers the injection is aware of the patient's treatment assignment with respect to three groups but is unaware of the dose of panitumumab. Other personnel (except for those assisting with injections), patients, and personnel at the central reading center are unaware of the patient's treatment assignment.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
1. Change in the retinal thickness in the foveola, as measured from Bruch´s membrane to the inner limiting membrane (i.e., including the retinal pigment epithelium layer), measured using optical coherence tomography (OCT) of the macula and optic nerve head at the time of the injections/re-injections
2. Best Corrected Visual Acuity (BCVA) measured using eye chart (ETDRS chart) at the time of the injections/re-injections

Key secondary outcome(s))
At baseline, at the time of the injections and re-injections, and at study end using optical coherence tomography:
1. Area and volume of subretinal tissue (differentiated between the compartment above and beneath the RPE line), and macular intraretinal and subretinal edema.
2. Size of atrophic lesions (geographic atrophies)

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. Best corrected visual acuity of <0.30 (decimal)
2. Foveal retinal thickness (measured from Bruch´s membrane to the inner limiting membrane, i. e. including the retinal pigment epithelium layer) of >300μm
3. Normal intraocular pressure
4. Transparent optical media
5. Absence of any other eye disease (except for cataract or pseudophakia)
6. No previous retinal or vitreoretinal surgery (except for peripheral retinal argon laser coagulation)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
55 years

Upper age limit
120 years

Sex
All

Key exclusion criteria
1. Inability to attend the follow-up examinations
2. Inability to understand the purpose and structure of the study.

Date of first enrolment
01/12/2023

Date of final enrolment
31/10/2026

Locations

Countries of recruitment
Russian Federation

Study participating centre
Ufa Eye Research Institute
90 Pushkin Street

Ufa
Russian Federation
450008

Sponsor information

Organisation
Ufa Eye Research Institute

ROR
https://ror.org/04grwn689

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Ufa Eye Research Institute

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and / or analyzed duringbe available upon reasonable request to the investigators (Prof. Mukharram Bikbov (Bikbov.m@gmail.com); Prof. Jost B. Jonas (Jost.Jonas@medma.uni-heidelberg.de)

IPD sharing plan summary
Available on request