Full title of study: **A pilot study to examine the safety and efficacy of intravitreal ranibizumab/ dexamethasone administration and oral minocycline in addition to Visudyne (verteporfin) photodynamic therapy for subfoveal choroidal neovascularisation secondary to age related macular degeneration: an open label trial**

EudraCT Number: **2006-004292-35**

Name of main REC: **King's College Hospital NHS Foundation Trust**

REC reference number: **06/Q0703/172**

Date of favourable ethical opinion: **29/01/2007**

Sponsor: **King's College Hospital NHS Foundation Trust**

Principle Investigator: **Ms S.Sivaprasad**

Study start date: **June 2007**

Study completion date: **October 2008**

Ethical Conduct of the study **This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki**

This study was performed in compliance with Good Clinical Practice.

Introduction

Age related macular degeneration (AMD) is a disease that is the leading cause of severe visual loss in the elderly in the UK. The region of the eye that is affected by the disease is the macula. This area is specialised for providing detailed vision. Two basic forms of the disease exist; the wet form and the dry form. Rapid deterioration of vision occurs in the wet form of the disease. This occurs due to abnormal blood vessels behind the retina, leaking fluid and blood into the central area of the retina. The abnormal blood vessels are called choroidal neovascularisation (CNV). The development of the abnormal blood vessels are initiated and encouraged by inflammatory mediators.

Study Objectives

To assess the safety and effectiveness of the combined therapy of intravitreal ranibizumab and dexamethasone, oral minocycline and verteporfin photodynamic therapy for subfoveal choroidal neovascularisation (CNV) secondary to age related macular degeneration (AMD).

Scientific Rationale

The cause of macular degeneration is not known, but it is known that many factors contribute to the final result in wet AMD which is the development of abnormal blood vessels. These factors involve cytokines and complex molecular reactions with a delicate balance between stimulatory and inhibitory factors. Combined therapy, using agents that act at different points in the pathological pathway and therefore synergistically have the potential to be more efficacious than monotherapy. This concept is gaining ground and clinical trials are underway investigating a number of combination modalities.

INVESTIGATIONAL PLAN

Study Design

Case series

Single Centre and Site

King's College Hospital, Denmark Hill, London SE5 9RS

Funding

The research was supported by a grant from Novartis Pharmaceuticals UK

Number of patients

20

Size of Study and Statistical power calculation

As this was a pilot study the number of patients to be included in the trial was not arrived at with a power calculation. As wet AMD is a variable condition in respect to presentation and response to treatment, it was considered that twenty patients would be sufficient to ensure the treatment response could be assessed allowing for the variation in response to treatment. A statistician has not given an opinion about this research.

Population demographics

Patients of either sex, any race, aged 50 years or older with a diagnosis of subfoveal CNV secondary to AMD are eligible.

Ethics and Regulatory Approval

The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice and all of the applicable regulatory requirements. King's College Hospital NHS Research Ethics Committee reviewed and approved this research trial.

Quality Assurance and Data Handling

Copies of protocols, Case Report Forms, physiological test results, correspondence, informed consents and other documents relevant to the study were kept on file by the Principal investigator and archived after completion of the study. The results of the study have been disseminated and presented at scientific conferences, with the aim of publication in peer reviewed scientific journals.

Selection of study population

The patients were identified by doctors working in the weekly photodynamic therapy (PDT) clinic. They were then referred to the researcher and if all inclusion criteria met invited to take part in the clinical trial following full discussion of what is proposed and involved in the trial. If the patient agrees to be involved then they were enrolled in the trial.

Inclusion Criteria

1) The patient must be willing to give written informed consent.
2) The patient must be able to undertake the necessary tests and treatment and be willing to be followed up.
3) Age 50 years or older
4) Clinical diagnosis of AMD
5) Subfoveal CNV on fluorescein angiography
6) LogMAR best corrected visual acuity of 24-73 letters on ETDRS chart

Exclusion Criteria

1) Inability to understand or sign consent form
2) The patient has a current medical condition or history of a medical condition that would be likely to preclude scheduled study visits such as unstable angina, dialysis, and active cancer.
3) Patient has a current ophthalmic condition or history of an ophthalmic condition that might compromise the assessment of the treatment such as diabetic retinopathy, uvetitis, amblyopia, ischaemic optic neuropathy
4) Signs of a myopic retina or refraction of > -8 diptres in their current or any previous glasses prescription
5) Signs of other retinal conditions that may have caused the CNV such as angioid streaks, choroidal rupture, and old chorio-retinitis
6) Open angle glaucoma
7) At increased risk of developing glaucoma such as having pigment dispersion syndrome or pseudoexfoliation
8) Unable to have a good quality fluoroscein angiogram taken eg. Due to head Tremor or media opacity
9) Allergic to fluoroscein or verteporfin
10) Previous treatment for a retinal detachment
11) Judged by the examining clinician to be at increased risk of retinal detachment due to weaknesses in the peripheral retina
12) Previous photodynamic therapy or other therapy for a CNV including argon laser treatment
13) Patient is currently participating or has participated in a clinical trial that utilized an investigational drug or treatment within 30 days prior to enrolment to this study
14) Patients taking anticoagulation therapy such as warfarin, with the exception of aspirin and other anti-platelet therapy
15) Exclusion of women of childbearing potential

16) Exclusion of pregnant or lactating women

Withdrawals

The patients were withdrawn from the study for the following reasons:

1) The patient withdraws informed consent to participate in the study
2) Adverse events that preclude continuation in the study
3) The patient fails to attend study visits (after attempts to contact the patient have failed)
4) The investigator, sponsor (Novartis) for any reason stops the study
5) If it is deemed in the best interest of the patient, for any reason
6) Death

Investigational Drugs

Active drugs: 1) Dexamethasone 200µg (in 0.05ml) for intravitreal injection,

2) Ranibizumab 0.3mg for intravitreal injection,
3) Verteporfin PDT (Visudyne®) Two step process:
    i. 10 minute intravenous infusion of Visudyne at a dose of 6mg/m^2 body surface area, diluted in 30ml infusions
    ii. Light activation of Visudyne at 15 minutes after the start of the infusion with a diode laser to deliver a light dose of 25J/cm^2
4) Minocycline 100mg daily orally for 3 months (Acnamino MR®)

Reference drugs: None

Schedule of Procedures

Visit number	Visit 1 Screening and treatment	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
Study month	0	1	2	3	4	5	6	7	8	9	10	11
Procedure												
Informed Consent	X											
Medical history	X											
BCVA	X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmic examination	X	X	X	X	X	X	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X	X	X	X	X	X
Colour fundus photo	X						X					
FFA	X						X					
BP	X											
Weight	X											
Height	X											
PDT & Visudyne	X											
Minocycline	X											
Dexamethasone	X											
Lucentis	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]

[1]Only to be administered if patient meets criteria for re-treatment at visit

Treatment Schedule

Eligible consented patients received a reduced light dose (25J/cm^2) verteporfin photodynamic therapy, an intravitreal injection of 0.3mg ranibizumab and 200µg dexamethasone at their first visit. Minocycline 100mg po was taken daily for 3 months. From month 1 to 11, patients received monthly ranibizumab injections if:
Best corrected visual acuity (BCVA) deteriorated by more than 5 letters compared to the BCVA at baseline or the previous month or retinal thickness at the central subfield as assessed by OCT, increased more than 100µm compared to the thickness from the previous month. During the 12 month study duration, a maximum of 12 ranibizumab injections and 1 verteporfin PDT could be administered. At each visit each patient underwent a test of visiual acuity using standard charts (logMAR), clinical slit lamp examination of the retina, measurement of macular thickness using ocular coherence tomography (OCT).

Injection protocol

Sterile technique

Instil topical anaesthesia, clean skin and ocular surface with betadine/povidone iodine. Drape with a sterile drap. Insert eyelid speculum. Inject 3.5mm from the limbus in a pseudophakic patient, 4mm in a phakic patient. G. Choramphenicol was administered 4 times a day for 5 days post procedure.

Evaluation criteria

Primary endpoint

Evaluate the changes in visual acuity from baseline at 12 months in patients treated with intravitreal ranibizumab in combination with verteporfin photodynamic therapy.

Secondary endpoints

The secondary efficacy variables will include:

Mean change from baseline in best corrected visual acuity (BCVA) at month 6

Proportion of patients who gained ≥ 5, 10, 15 letters of BCVA from baseline at months 6 and 12

proportion of patients who lose less than 15 letters of BCVA from baseline at months 6 and 12

Mean change from baseline in total size of lesion and total size of CNV at 3, 6 and 12 months

Change in area of leakage at 3, 6 and 12 months

Total number of treatments of Ranibizumab

Mean time to first re-treatment following the initial combination therapy

Mean change in retinal lesion thickness by OCT at centre of fovea at 3, 6 and 12 months

Re –treatment Criteria

Re-injection with 0.3mg of Ranibizumab was indicated if any of the following were present at the monthly follow up visits:

1) A loss of > 5 letters of refracted logMAR BCVA recorded on the modified ETDRS chart when compared to the previous month
2) An increase of central retinal thickness greater then 100µm measured on the OCT fast macular thickness map when compared to the previous month
3) Fresh macular haemorrhage on dilated fundus biomicroscopy

Safety Monitoring

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

The summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)

The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

Results in death;

Is life-threatening;

Required hospitalisation or prolongation of existing hospitalisation;

Results in persistent or significant disability or incapacity;

Consists of a congenital anomaly or birth defect.

Reporting Responsibilities

King's College Hospital NHS Foundation Trust delegated the Sponsor responsibilities of Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the Joint Clinical Trials Office (JCTO).

All SAEs, SARs and SUSARs were reported by the Chief Investigator to the JCTO in accordance with current Pharmacovigilance Policy.

Death as a result of disease progression and other events that are primary or secondary outcome measures were not considered SAEs and were reported on the appropriate case report form.

The JCTO reported SUSARs (suspected unexpected serious adverse reactions) and other SARs to the regulatory authorities (MHRA, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator reported to the relevant ethics committees. Reporting timelines were as follows:

-SUSARs that are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days

-SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction

The Chief Investigator will provide an annual report of all SARs (expected and unexpected), and SAEs that will be distributed to the Sponsor, JCTO, MHRA and the REC.

In addition, the Chief Investigator will report any serious adverse event during the trial period and for a period of 4 weeks after to Novartis. All patients with a SAE were followed up and the outcomes reported.

Safety was assessed by tonometry, visual acuity, ophthalmic examinations, adverse events and vital signs.

Serious unexpected adverse event report

Report of extradural haematoma

89 year old patient with past medical history of breast cancer, left mastectomy, transient ischaemic attacks, atrial fibrillation and allergy to penicillin. The patient received study medications on 10/09/07 and on 1/11/07 when the last dose was administered. The patient was on concomitant warfarin, dose and duration not specified. On 26/11/07 the patient experienced the event, collapsed and was hospitalized. An MRI of the spine revealed an acute extradural bleed, with prolonged INR values which was corrected with fresh frozen plasma and vitamin K supplements. The patient died on 8/12/07. Cause of death was reported to be extradural haematoma, considered by the investigator to be possibly related to study drug ranibizumab. The event was reported to the sponsor Novartis who confirmed that neither Visudyne or ranibizumab associated cases of extradural haematoma have been previously reported and that this event is therefore considered unexpected for ranibizumab and Visudyne (verteporfin) photodynamic therapy. The event was reported to King's College Hospital and the sponsor notified the REC according to standard operating procedures. The SUSAR was also reported to the MHRA as per regulations.

Substantial Amendment Clinical Trial Protocol

An amendment for the study was submitted to the MHRA in July 2008 and also to King's College hospital REC. The amendment was due to a change of chief investigator, a change of sponsor contact details and administrative changes to the protocol to clarify pharmacovigilence reporting and trial management procedures. It also reflected a change of IMP supply (minocycline), clarification in the protocol of specified brand for other IMPs and confirmation of QP release for Ranibizumab.

Advice was also sought from the MHRA in June 2008 as the sponsor's IMP did not have QP release. At this stage recruitment for the trial was completed but there were still active participants on the trial. The MHRA Clinical Trials Unit Assessor confirmed that withdrawing patients and treating with commercial stock was correct and complied with the regulations. It was suggested rather than withdrawing patients from the trial they should be suspended and then subsequently re-entered.

Results

Nineteen eyes of nineteen patients were recruited into the study. Three patients were withdrawn from the study (two at visit 10 and one at visit 8) due to non availability of ranibizumab (0.3mg in 0.05ml). The investigators continued to monitor these patients and treated them with 0.5mg/ 0.05ml ranibizumab if re-treatment was required. Fifteen eyes completed the study.

Baseline demographic characteristics of the 15 eyes that completed the study

Baseline characteristics	**Number of eyes (15)**
Mean age in years	79.3 ± 6.4
Laterality (OD:OS)	9:6
CNV type	
Predominantly classic	3
Minimally classic	3
Occult	8
Retinal angiomatous proliferation	1
Mean baseline logMAR visual acuity (ETDRS letters)	57.1 ±10.6 (range 31-73)
Mean baseline CRT in microns	326.8 ± 63.6 (range 214-430)
Mean angiographic lesion size in mm^2	7.02 ± 2.74 (range 3.5- 10.9)

Summary of the main study outcomes

Study Outcome	**Result**
Mean change in logMAR acuity during study	-4.4 ± 11 ETDRS letters
Number of eyes losing or gaining <15 ETDRS letters	13/15 (86%)
Number of eyes gaining ≥ 5 ETDRS letters	3/15 (20%)
Number of eyes losing ≥ 15 ETDRS letters	2/15 (13.3%)
Mean change in CRT	70µm ± 80.7
Mean number of ranibizumab re-treatments following baseline combination therapy	2.2 (range 1-6)

Baseline characteristics of the subgroup that showed no change or any improvement in vision compared to the subgroup that lost any letters

Change in ETDRS Vision during study	**Mean logMAR acuity**	**Mean CRT in microns**	**Mean lesion size in mm^2**
Gain of 0 to 12 letters	59.3	338.9	6.13
Loss of 4 to 30 letters	55.3	316.3	7.79

Discussion

Ranibizumab monotherapy is the current recommended treatment for wet age related macular degeneration. It is administered as a course of intravitreal injections as a loading course of three injections for three months followed by additional injections if indicated. Patients are monitored at monthly intervals for changes in visual acuity, clinical and OCT appearance to determine the need for retreatment. Retreatment with ranibizumab is indicated if there is a loss of greater than 5 letters on BCVA, new retinal haemorrhages, and/or an increase in central retinal thickness of >100µm on OCT. Treatment usually continues indefinitely unless vision falls below 15 ETDRS letters, there is evidence of continued deterioration despite treatment, or permanent damage to the fovea. The estimated mean number of ranibizumab injections per patient per year is between six and eight.

The main drawbacks of prolonged and frequent intravitreal anti VEGF therapy are:

1) The failure to target the complex pathology of exudative AMD
2) Detrimental effects of chronic VEGF blockade
3) Cumulative risks of the intravitreal procedure
4) Frequent hospital visits for elderly patients
5) Increased volume of patients attending clinics
6) Cost implications

The main aims of the study were to assess the efficacy and safety of a multitherapeutic approach to treating the CNV with the aim of reducing the mean number of ranibizumab injections required.

Photodynamic therapy (PDT) was the first treatment to be of clinical benefit for most patients with subfoveal neovascular AMD. PDT was approved by the Food and Drug Administration (FDA) in 2000 for the treatment of predominantly classic subfoveal lesions associated with AMD. In 2004, the treatment was expanded to include occult and minimally classic lesions. Standard photodynamic therapy is a two-step process involving an initial intravenous infusion of verteporfin followed by irradiance with a 689nm laser for 83 seconds beginning 5 minutes after completion of the infusion delivering a total energy of $50J/cm^2$. Verteporfin binds to low density lipoproteins (LDL) in the plasma during the infusion, which are then preferentially bound by choroidal neovascular tissue which expresses LDL receptors. Irradiation of the neovascular lesion by the laser creates toxic oxygen species that induce thrombosis and closure of the choroidal neovascularisation. Although the thrombosis occurs predominantly in the choroidal neovascularisation, there is evidence of damage both to the choriocapillaris and the RPE [1]. The thrombotic effect of PDT is short lived, and typically within 10-14 weeks there is reperfusion of the neovascular lesion. Evidence of leakage on fluoroscein angiogram is the indication for retreatment. Over 1 to 2 years of treatment, the frequency of leakage, and therefore treatment, typically decreases.

The first clinical trial to demonstrate the efficacy of PDT was the Treatment of Age Related Macular Degeneration with Photodynamic Therapy (TAP) Study which examined classic subfoveal AMD lesions [2]. The primary endpoint was the loss of less than 15 letters or 3 lines on the ETDRS chart, which was defined as moderate visual loss. After both 1 and 2 years of follow up, treated eyes suffered less visual loss than controls. An extension of the TAP Study demonstrated that these treatment benefits are maintained for up to 36 months [3]. The Verteporfin Photodynamic Therapy (VIP) study examined lesions with either occult with no classic CNV or classic CNV with baseline vision of 20/40 or better [4]. The same moderate visual loss endpoint was used. At 1 year, there was no benefit in the primary endpoint compared with controls for all lesions. By 2 years, there was a benefit. The Verteporfin in minimally classic CNV (VIM) Study examined the effects of both reduced fluence and standard fluence in minimally classic lesions. This study suggested that reduced fluence may be beneficial in such lesions [5].

Reduced fluence PDT with 25J/cm^2 reduces choroidal hypoperfusion, inflammation , vascular leakage and VEGF upregulation that is associated with standard fluence PDT[1]. Reduced fluence PDT was used only once during the study. Anti-inflammatory agents such as intravitreal triamcinolone have been used as an adjunct for PDT to limit further VEGF upregulation initiated by the therapy. This combination therapy has been shown to be beneficial when compared with PDT monotherapy in terms of functional results. [7,8]. However, triamcinolone has been associated with increased risk of cataract formation [9] and raised intraocular pressure [10]. It was not until recently that replacement of triamcinolone with dexamethasone was considered [11]. Triamcinolone that is injected as a suspension has prolonged effects, particularly with regard to raised intraocular pressure. Dexamethasone which is injected as a solution, is more rapidly cleared from the vitreous, as there is no sustained release due to suspension, there is reduced risk of steroid induced side effects.

Dexamethasone has anti-inflammatory, anti-fibrotic and anti-VEGF effects [6,12,13]. Further, its antiproliferative effects are reduced in the presence of VEGF [14] so combination of dexamethasone with anti-VEGF therapy may assist with dexamethasone's antiproliferative effects. Dexamethasone may reduce endothelial dysfunction and inhibit VEGF induced vascular dysfunction [15]. At the molecular level, dexamethasone exerts its anti-inflammatory effect by interfering with the activation of pro-inflammatory genes without affecting factors that inhibit inflammation [16].

Minocycline is a semi-synthetic derivative of tetracycline with a longer half life and improved penetration through the blood brain barrier. Apart from its antimicrobial actions it also has potent anti inflammatory and immunomodulatory effects [17]. Minocycline possesses antioxidant activity and inhibits both free radical production and lipid peroxidation in a concentration dependent manner [18]. Minocycline has been shown to protect melanocytes from apoptotic induced oxidative stress in vitiligo, a progressive disorder manifested by the selective destruction of melanocytes in the skin [19]. Leung et al [20] investigated whether minocycline and its structurally related analogues would protect photoreceptor cells in primary bovine culture from light and oxidative stress. Minocycline was shown to protect photoreceptors in culture but within a narrow therapeutic range of concentrations. It was postulated that Minocycline may act as an adjunct for neovascular AMD in the combined treatment regimen. A reduced dose of ranibizumab (0.3mg in 0.05mls) was used given the combined angio-occlusive effect of PDT and the effects of dexamethasone and minocycline.

Conclusions

The study regimen reduced the intravitreal ranibizumab re-treatment rate per study eye over the 11 month follow up to 2.2 injections while the total number of ranibizumab injections per study eye was 3.2. Therefore the combination regime was successful in reducing the total number of ranibizumab injections required to treat a patient with wet AMD. The average number of months from baseline treatment with combined reduced

fluence PDT, ranibizumab, dexamethasone and minocycline to retreatment with ranibizumab monotherapy was found to be 2.6 (range 1-6 months) with only 2 eyes requiring retreatment at the one month follow up visit. This suggests there may be a possibility of increasing the first clinic visit following initial baseline therapy from one month to two months. Although 13/15 or 86% of eyes maintained stable vision, only 20% eyes gained ≥ 5 letters. The final visual outcomes were therefore less good than those seen in clinical trials of ranibizumab monotherapy [21, 22]. The improvement in acuity achieved early in the study failed to be maintained and was followed by a sharp fall at month 8. This is reflected in the mean loss of 4.4 ETDRS and the failure of any study eye to gain ≥ 15 letters. The results suggest that combination therapy allows reduction in the number of Ranibizumab required to stabilize vision in most patients. However, the final gain in vision is less than that achieved through more intensive ranibizumab treatment regimes.

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