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Safety of intravitreal ziv-aflibercept in patients with diabetic macular edema, macular edema following retinal vein occlusion and neovascular age related macular degeneration in a Ghanaian population: A phase I randomized interventional study

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ABSTRACT

Brief Background: Retinal vascular diseases are a significant cause of visual loss world-wide, including Ghana. Anti-vascular endothelial growth factor (anti-VEGF) such as aflibercept, ranibizumab and bevacizumab have become the standard of care for diabetic macular edema (DME), macular edema (ME) following retinal vein occlusions (RVO), and neovascular age related macular degeneration(nvAMD). Aflibercept has been approved by the United States of America (USA) Food and Drug Administration (FDA) for the treatment of DME, nvAMD, and ME following RVO. The recommended dose of intravitreal aflibercept is 2mg in 0.05ml administered monthly or initial monthly injections for the first 3 months followed by 2 monthly injections. Aflibercept is highly expensive (USD1850 per dose) and not available in many developing countries including Ghana. Ziv-aflibercept, a molecule structurally identical to aflibercept but differs due to its formulation with hyper-osmolality has been approved by the USA FDA for the treatment of metastatic colorectal cancers. Ziv-aflibercept, used off-label, has been found to be safe in patients with DME and nvAMD in phase 1 trials at a dose of 1.25mg in 0.05ml. The cost of compounded ziv-aflibercept is much reduced to USD 67 per dose. The 1.25mg dose of ziv-aflibercept is below that recommended for intravitreal injections of aflibercept. However, to the best of our knowledge, there are no data available on the safety of 2mg of ziv-aflibercept, although *in vitro* studies indicate that it is safe. Furthermore, there is no data on the intravitreal administration of ziv-aflibercept in the Ghanaian population to date.

Aim: To evaluate the safety of 1.25mg and 2mg ziv-aflibercept in Ghanaian population with retinal vascular diseases.

Methodology: This is a prospective, randomised, double masked, phase 1, interventional study. Twenty (20) patients with centre involving DME, ME following RVO, and nvAMD will be assigned to 2 groups: 1.25mg/0.05ml (control) and 2mg/0.08ml ziv- aflibercept and will receive 3 doses of ziv-aflibercept at 4 weekly intervals. Intraocular pressure will be determined 30 minutes following injection and in subsequent visits. Safety data will be collected at days 1and 7 after initiation of treatment, and at 4, 8 and 12 weeks.

Primary outcome measures are ocular safety parameters- including the incidence of pain, blurred vision, raised intraocular pressure, intraocular inflammation and endophthalmitis(eye infection), as well as systemic safety at 4 weeks.

Secondary outcome measures are ocular and systemic safety parameters at 12 weeks, change in BCVA (ETDRS letters), central subfield foveal thickness (CSFT) and central retinal thickness (CRT) as measured on optical coherent tomography (OCT) at 4 and 12 weeks.

Expected Outcome: We seek to evaluate the safety of 2 different doses of ziv-aflibercept in patients with DME, ME following RVO and nvAMD in a Ghanaian population. We expect that there will be no differences in safety between the 2 doses of ziv-aflibercept.

EXTERNAL LINK

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THIS PROTOCOL ACCOMPANIES THE FOLLOWING PUBLICATION

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Protocol safety of ziv aflibercept Ghana.docx

Randomisation process and Procedures

1 Comprehensive ocular examination will be repeated at day 1 and 7 after the initial anti-VEGF injection and in all subsequent visits. All patients will undergo fundus photography (ZEISS 450 FUNDUS CAMERA, ZEISS INC. JENA, GERMANY), Fluorescein angiography (ZEISS 450 FUNDUS CAMERA, ZEISS INC. JENA, GERMANY)) and spectral domain optical coherence tomography (SD-OCT) (TOPCON 2000, TOKYO, JAPAN) at baseline. Fundus photography and SD-OCT will be repeated on days 7 and 28 and in all subsequent visits as per study protocol.

2 Systemic arterial blood pressure, fasting lipids and fasting blood sugar will be measured at baseline. Systemic arterial blood pressure and fasting blood sugar at visits on days 1, 7 and 28.

3 After obtaining informed consent, all eligible patients will be randomly assigned to either 1.25mg or 2mg ziv-aflibercept using simple random sampling which involves picking 2 labelled cards from an envelope by an individual independent of the study investigators, but the treatment is concealed to the patients.

4 Preparations of Ziv-aflibercept injections: To minimize the risk of repeated puncture of the vial, the vial containing 100mg/4ml of ziv-aflibercept will be punctured once under the laminar air flow system at the pharmacy manufacturing unit of KBTH and withdrawn using 5µ microfilter in 0.1ml and 0.15ml aliquots into 1 ml syringes, labelled and each syringe kept in separate sterile plastic wrappers (Eye Drape plus, Aurolab, India) and are immediately stored at 4 degrees Celsius. Two (2) syringes containing the withdrawn samples shall be cultured on chocolate agar and sabouraud agar by MDS-LANCET laboratories ltd. Negative culture report shall be received before the remaining samples will be released for injection. The first syringe and the last drawn product shall be sent for microbiologic studies. Each time the vial is to be used we shall inspect the syringe physically for contamination or change in colour. The stored ziv-aflibercept in 1ml syringes shall be used within 2 weeks from the date of preparation. Omek et al (2008) found that storage and multiple use of anti-VEGF from single-use vials does not seem to result in microbial contamination for up to 15 days from initial use.

5 Intravitreal injection procedures: Standard precautions relating to intravitreal injections shall be observed. Patients will be pooled together for Injections once per week. An unmasked certified physician, will give the intravitreal injections. The intravitreal injection will be done using a sterile technique. Topical anaesthetic agent proparacaine and 5% povidone iodine will be instilled into the conjunctival cul-de sac and periocular skin, eyelids and lashes will be cleaned using 10% povidone iodine. The eye will be draped and the injection given into the mid vitreous cavity 4 mm or 3.5mm posterior to the limbus in phakic and pseudophakic eyes, respectively. Hand motion vision is checked and confirmed to be present. No topical antibiotics will be given prior to, during or after each injection.

6 Follow up examinations: Intraocular pressure (IOP) will be checked at 30 minutes after intravitreal injection and at subsequent visits (on day 1, 7 and 28) by the examining physician (IZB) who will be masked to the treatment doses. The examining physician (IZB) will also assess each patient for ocular and systemic adverse events on days 1, 7 and 28 after initial injection. Ocular adverse events include incidence of raised intraocular pressure (>21mmHg), corneal abrasions, cataracts, and intraocular inflammation. Systemic evaluations include systemic arterial blood pressure, fasting lipids and fasting blood sugar measured at baseline and at visits on day 1 and 7. Systemic arterial blood pressure will be measured in all subsequent visits. Each patient will receive 3 doses of ziv-aflibercept at 4 weekly intervals. At 12 weeks, the anatomic response of the patients to anti-VEGF will be assessed by an independent investigator (WMA) based on the change macular morphology using SD-OCT.

SCHEDULE OF EVENTS TABLE.docx

7 SAMPLE SIZE: 20 eyes will be included in this study. Only One eye per patient will be included in the study. Where both eyes are eligible, the eye with the worse visual acuity will be selected for the study.

Outcome measures

8 To date, no serious ocular or systemic adverse event have been reported with intravitreal ziv-aflibercept injection (8-14, 21, 22, 33) although these studies are short-term with small numbers. The only minor adverse event related to intravitreal injection of ziv-aflibercept was conjunctival thinning which occurred in 1 eye of 12 patients with nvAMD and resolved on administration of topical antibiotics.(8) In a comprehensive review(Meta-analysis) of the ocular and systemic safety of intravitreal aflibercept in 10 phase II and phase III clinical trials of patients with DME, ME following retinal vein occlusion and nvAMD using person-years at risk methodology, Kitchens et al demonstrated that eyes treated with intravitreal aflibercept injection were not at increased risk of intraocular inflammation or endophthalmitis, had lower rates of hypertension and differences observed with serious adverse events(SAEs) and APTC-ATEs were consistent with chance variations.(38) They concluded that the rate of ocular and systemic adverse events with intravitreal aflibercept injection (IAI) were similar to controls and across disease states. (38) In an analysis of 2 phase III trials using 2mg dose of aflibercept every 4weeks, Freund et al reported that the proportion of eyes with IOP>21mmHG at 96 weeks visit was 14.2%.(39)

9 The primary outcome measure to be evaluated in this study is safety of intravitreal ziv-aflibercept at 4 weeks. Ocular toxicity will be assessed based on the number of ocular adverse events such as blurred vision (mild-loss of 0.1logMAR, moderate- loss of 0.2 logMAR and severe- ≥ 0.3 logMAR), raised intraocular pressure (>21mmHg), corneal abrasions, cataract, intraocular inflammation and endophthalmitis (eye infections) using a predesigned questionnaire (Appendix III case report form)

Appendix III CRF safety of ziv aflibercept.doc and SD-OCT findings.

10 Corneal abrasion- An area of corneal epithelial defect assessed on slit lamp biomicroscopy after instillation of fluorescein eye drops, before any applanation tonometry is performed.

11 Cataract- presence of Nuclear sclerosis, cortical, posterior subcapsular, anterior capsular. This will be assessed using slit lamp biomicroscope after pupil dilatation.

12 Intraocular inflammation/endophthalmitis will be assessed by the degree of anterior camber cell, flare, aqueous fibrin and hypopyon, vitreous cells and haze(vitritis), vasculitis and choroiditis using the standardised uveitis nomenclature (SUN) working group classification.(40) Inflammation in the anterior segment is determined by assessing the cell count and flare at baseline and at subsequent visits. The assessment is based on number of cells in the anterior chamber(AC) in a 2mm long X 1mm wide slit beam with maximal light intensity and magnification. The slit beam is directed at 45 degrees to the iris plane. Grading of cell and flare will be done according to the grading scale in Appendix III. Vitritis will be assessed using the grading scale in appendix III- table2. The definitive proof of endophthalmitis is dependent on vitreous biopsy and microbiological evaluation (microscopy, culture).

13 Posterior vitreous detachment(PVD)- is a condition where the gel-like substance that occupies the space between the retina and the lens of the eye liquefies and separates from the retina. PVD is diagnosed by slit-lamp biomicroscopy, which will usually show a prominent plane defining the posterior vitreous face. The plane is seen in the form of inverse S-shaped in the anterior vitreous cavity. The presence of a glial annulus in the vitreous cavity (Weiss ring) is strong evidence of PVD. The presence of PVD will be assessed by slit lamp biomicroscopy, fundus biomicroscopy with 90D/78D lenses and indirect ophthalmoscopy with +20D lens. In the Presence of PVD, peripheral retinal examination with indirect ophthalmoscope with scleral indentation is mandatory.

14 Pain severity scale- Eye pain will be assessed using the eye sensation scale (Caudle et al. 2007) The eye sensation scale is divided into 5 categories : none, mild, moderate, severe and extreme(Appendix III – CRF) .

15 Systemic adverse events will be assessed based on systemic evaluation using predesigned questionnaire (Appendix III). Systemic adverse events will be initially assessed based on history and confirmation from patient's physician or from the physician for this study (EK).

16 Secondary outcome measures are occurrence of ocular and systemic adverse events at 12 weeks (Appendix I and II) such as IOP>25mmHg, increased IOP > 10mmHg and >15mmHg from baseline, change in BCVA (logMAR), BCVA improvement of at least 0.1 logMAR, BCVA improvement of at least 0.2 logMAR, BCVA improvement of at least 0.3 logMAR, BCVA worsening of at least 0.3 logMAR, central subfield foveal thickness (CSFT) and central retinal thickness (CRT) using SD-OCT at 4 and 12 weeks.

17 The toxicity grading Scale that will be used to assess the safety of ziv-aflibercept will be based on the severity of the outcome measures outlined above and include mild, moderate, severe and potentially life-threatening and death (Appendix IV- Toxicity grading scale) scale APPENDIX IV TOXICITY- ADVERSE EVENTS GRADING.docx

Data Handling

18 Patients' data will be recorded using a pre-designed questionnaire. The records of participating patients will be kept in a secured cabinet with only the principal investigator having access to the cabinet. The Senior research assistant will be responsible for data entry. Computer designated for data entry will be password protected and only the data entry manager and principal investigator will have access to the computer. The use of the computer for internet surfing will be prohibited. All data entry will be proofed for accuracy by the principal investigator by visual proofing of the case report form(CRF) and cross-referencing with source documents (thus, SD-OCT, Fundus photographs, fasting blood sugar and lipid print outs). All data will be captured and cleaned using predesigned Microsoft excel version 2015 by the Senior research assistant and principal investigator. Patients' data will be handled by strict adherence to the data protection act and the Health insurance portability and accountability act. Scanned and keyed data will be saved in a designated computer and backed up onto external hard disc drive and flash disc every 2 weeks. The only data that will be transmitted via a secured internet website are Fundus photographs, fundus fluorescein angiograms and SD-OCT for analysis by independent investigator (WMA). The images will be anonymised by given each image unique codes before transmission via the University of Nottingham Website to the independent investigator. The independent investigator shall establish and maintain the confidentiality and security measures necessary to ensure the integrity of the transmitted data in accordance with measures specified in the data protection Act. At the close of the trial the principal investigator shall retain control of both manual and electronic records and ensure proper archiving of the records. All relevant electronic records shall be stored in an external hard disc drive and the case report forms, consent forms, study files, fundus photographs and SD-OCT reports shall be archived at the medical records department in a secured cabinet for 2 years after the close of the trial. All other data related to the trial stored in the designated computer shall be destroyed.

Statistical analysis

19 All statistical analyses for this study will be done using STATA 13 (Statacorp, Texas, USA). The frequencies of ocular and systemic adverse events and serious adverse events will be computed. Continuous variables will be presented as mean and standard deviation. Pre- and post-injection changes in BCVA, intra ocular pressure, and central subfield foveal thickness will be compared using paired t-test. ANOVA and MANOVA will be used to assess the repeated measures at times 0, 4, 8 and 12 weeks.A P value<0.05 will be considered statistically significant.

Statistical Plan

20 The unmasked statistician(EK) will analyse the data based on the following schedules: 1. after 50% of subjects have been recruited and followed for 1 month 2. after 100% of subjects have been recruited and followed up for 1 month. 3. After 100% of subjects have been recruited and followed up for 3 months. The interim analyses will include demographic and baseline characteristics by group, analysis of subjects screened, enrolled, active, completed and terminated, and primary outcome endpoints including the incidence of pain, blurred vision, raised intraocular pressure, cataract, intraocular inflammation, endophthalmitis, and systemic adverse events by group. The data will be presented by masked treatment groups to the data and safety monitoring board (DSMB) and a decision on early stopping or continuation of the trial taken in the event of occurrence of large differences or serious adverse events observed in the interim analysis.

21 Adverse Event Reporting : On suspicion of adverse events, the event will be recorded in the adverse event report book and the principal investigator will be notified immediately. Investigations will be carried out to determine the duration, likely cause of the adverse event, mitigating measures and a report generated by the principal investigator and unmask statistician. The members of the Data and Safety Monitoring Board (DSMB) will also be informed immediately and a meeting convened to determine the seriousness of the adverse event, the likely cause and a decision taken on modifications of the trial. A final report on the specific adverse event will be submitted to the chairman of the KBTH-IRB and the director of FDA Ghana will be duly informed on the occurrence of this adverse event and the decision taken by the DSMB regarding this issue. When adverse event is considered serious, a SAEs report form will be completed by the principal investigator and unmasked statistician and the DSMB will be notified within 24hrs. The study clinician will complete a SAE Form within the following timelines: • All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to DSMB within 24hrs awareness. Other SAEs regardless of relationship, will be submitted to the DSMB within 48hrs of awareness. All SAEs will be followed until satisfactory resolution. Other supporting documentation of the event may be requested by the DSMB and should be provided within 48 hours. The PI will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction within 48hrs after the PI's initial receipt of the information. In the event of occurrence of eye pain, the affected eye will be examined to exclude raised intraocular pressure and intraocular inflammation and the pain will be relieved with topical analgesic agents. Patient will be followed up for 7 days after cessation of the adverse event. In the presence of sterile inflammation topical corticosteroids will be prescribed and patient monitored daily for response to treatment or progression of the inflammation. When endophthalmitis is suspected, vitreous specimen will be taken for microbiology and intravitreal injection of antibiotics will be given followed by topical antibiotics and corticosteroids, patient monitored daily and treatment revised based on patients' response to treatment. The rescue treatment that will be given to participants in the event of exacerbation of the condition whilst on the IP and / or when there are symptoms of toxicity after IP administration will be bevacizumab. Although the use of bevacizumab is also off-label, its safety and efficacy has been established in land mark clinical trials.

Termination Rules

22 The study will be halted according to the following criteria: 1.Three adverse events classified as severe (grade 3) have been reported 2.One potentially life -threatening adverse event (grade 4) have been reported 3. Two or more cases of endophthalmitis have been reported from the same vial of injection. 4.Large differences in the mean change in acuity (≥ 0.3logMAR) between the groups 5.Serious violation/deviation deem to significantly affect the overall study outcome as determined by DSMB (protocol violation log Appendix VIII). The stopping rules for a particular participant include the following: participant has completed the study, occurrence of serious adverse event, lost to follow-up, non-compliant participant (especially if 4week visit missed), withdrawal of consent, and death. In the event of stopping of participant from the trial, an off study form(Appendix III CRF) will be completed and adverse event reporting form (Appendix III) will be completed if this due to occurrence of AE/SAE. The primary outcome measure will be determined at 4 weeks. If a patient leaves the trial after 4week visit the patients' data will be included in the analysis. If a patient leaves the trial prior to 4 weeks after enrolment that particular patient shall be replaced by another patient and their data shall not be included in the final analysis. The original randomisation process shall be utilised in the replacement of the patient if recruitment is not completed. No replacement will be allowed if enrolment of the required number of patients is completed. Where a patient stops the trial, the patient shall be followed for 30 days after the last injection or after resolution of adverse events. The data that shall be collected for every patient stopping the trial include Date of last injection, date off study, reason off study and/or adverse events (Appendix III) The principal investigator will inform the DSMB members within 24hrs of occurrence of serious adverse event and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing within 48hrs. The DSMB will provide recommendations for proceeding with the study to the principal investigator. The principal investigator will inform the KBTH-IRB and FDA of the temporary halt and the disposition of the study within 48 hours of receiving the report from the DSMB.

Protocol Violation

23 In the event of occurrence of protocol violation, a protocol violation log (appendix VIII) APPENDIX VIIIc- Protocol_Violation_Log_safety of ziv aflibercept v3.doc will be completed and the DSMB informed immediately. The DSMB shall convene a meeting within 48hrs to determine the effect of the protocol violation on the conduct and outcome of the study. The decision of the DSMB shall be communicated to the KBTH-IRB and FDA within 48hrs.

Data and Safety Monitoring Board

24 A data and safety monitoring board (DSMB) comprising of three members has been constituted. The members include a Chairperson, 2 other members and an executive secretary to the DSMB. The executive secretary shall have no voting right. He will attend only the open session and Confidentiality shall be strictly observed. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. The proposed DSMB charter is as shown in Appendix X. APPENDIX X-DATA SAFETY MONITORING BOARD and SIGNATURES.docx The DSMB shall meet before patient enrolment, 1 month after 50% of patient enrolment and at 3 months after 100% of patient enrolment or at any time as deemed necessary. Monitoring for this study will be performed by the DSMB to ensure that the rights and well-being of the enrolled patients are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, with Good Clinical Practice, and with applicable FDA Ghana requirements.