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Corticosteroid for Diabetic Macular Edema (DME) Study

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1.0 STUDY SUMMARY

Title: Corticosteroid for Diabetic Macular Edema (DME) Study

Objectives: Our current goal Of the continuation study is to study a subset of patients who have diabtic macular edema (DME) and are treated with regional corticosteroids. The study evaluates the effect of long acting and short acting intravitreal corticosteroid on the intraocular cytokine profile and its association with treatment response.

Hypothesis: Our central hypothesis is that inflammation mediators are biomarkers of DME in the aqueous and that regional corticosteroid application reduces/suppresses those inflammatory mediators thereby leading to resolution of DME.

Study Design: Longitudinal Cohort study

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2.0 ABBREVIATIONS

CFR	Code of Federal Regulations
CRF	Case Report Form
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
IRB	Institutional Review Board
SAE	Serious Adverse Events

3.0 INTRODUCTION

Nearly 300 million individuals have diabetes worldwide and the prevalence is rising. Over one-third of diabetic patients will develop diabetic retinopathy (DR). Five to 10% of these individuals will suffer from vision-threatening complications1. DR progresses in many patients despite preventable measures such as blood sugar and blood pressure control[2,3]. Other available treatments require invasive eye injections and are often ineffective—DR remains the leading cause of legal blindness among working-age adults1. Current diagnostic tests fail to identify early disease stages or predict disease progression. Consequently, new biomarkers and therapeutic strategies are needed.

A growing body of scientific evidence indicates that inflammation contributes to the pathogenesis of DR[4-8]. The retinal vasculature of diabetic humans contains increased numbers of leukocytes and breakdown of the blood-ocular barrier develops early in its course[5,9]. Both phenomena presumably lead to progressive dysfunction and death of endothelial cells and pericytes which are pathophysiological hallmarks of DR[10,11]. In support of this, a number of pro-inflammatory cytokines (products of leukocytes) are consistently elevated in the aqueous and vitreous of patients with advanced stages of DR and diabetic macular edema (DME)[12-16]**.** Chronic inflammation-mediated vascular disease then results in subsequent capillary non-perfusion, retinal ischemia, and vascular leakage that are key clinical features of advanced DR and result in irreversible vision loss[5, 17]**.**

DR is an established inflammatory disease with leukocyte involvement[4–8]. Chronic hyperglycemia induces expression of damaging adhesion molecules through many pathways. For example, intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 promote leukostasis (Figure 1)[9–12]. Early in DR, leukocytes dominate the retinal vasculature, and the blood-ocular barrier breaks down[8,13,14]. Both phenomena lead to progressive dysfunction and death of endothelial cells and pericytes, which are pathophysiological hallmarks of DR[15–19]. Many inflammatory cytokines (products of leukocytes) are consistently elevated in the aqueous and vitreous of patients with advanced DR and diabetic macular edema (DME)[20–27]**.** Chronic inflammation-mediated retinal vascular damage results in vascular leakage, capillary non-perfusion, and retinal ischemia; all key clinical features of advanced DR that lead to irreversible vision loss[8,28]**.**

Inflammatory mediators are candidates for direct biomarkers that may predict DR progression as well as treatment response. To date the only validated prognostic DR biomarker is the circulating glycemia marker glycated hemoglobin (HbA1c)[2,29]. HbA1c screening, however, reflects glucose control, which indicates disease risk as opposed to DR pathology[30] **.**

Prostaglandins (PGs) mediate an inflammation feedback loop associated with DR progression[31,32]. Five PG classes (PGE2, PGD2, PGF2α, PGI2, Thromboxane A2), are synthesized via cyclooxygenase enzyme (COX) from the polyunsaturated omega-6 fatty acid, arachidonic acid. COX, which is present in most retinal cell types, is upregulated in response to various inflammatory cytokines (Figure 2)[13,33–36]**.**

It is now well established that PGE2 is the predominant inflammatory PG class within the eye. In animal models of DR, retinal cells consistently upregulate COX and PGE2 [37,38]. PGE2 is increased by 40% in the retinal vasculature of diabetic rats and is significantly reduced by treatment with insulin[37]. PGE2 promotes vasodilation, disrupts the blood-ocular barrier, and facilitates leukocyte migration[33,39,40]. In DR, macrophages produce PGE2, which stimulates production of the pleiotropic cytokine, interleukin (IL)-641. The macrophage marker, CD14, also increases in the DME eye[42,43]. Notably, aqueous IL-6 levels correlate with DR progression[44,45]. In some experimental systems, COX activity also regulates release of IL-8, a potent and specific neutrophil chemoattractant[46,47]. Recruited neutrophils are thought to initiate and propagate vascular disease via endothelial cell injury[17]. Corresponding, neutrophils are overrepresented in choroidal and retinal blood vessels of diabetic eyes and IL-8 levels rise in the aqueous and vitreous of eyes with advanced DR[13,21,48,49].

The angiogenic factor VEGF mediates neovascularization and macular edema in DR[50,51]. Laser treatment, surgery and anti-VEGF therapy are current standard management of care options for late stage, proliferative DR[52]. Corticosteroids, through anti-inflammatory actions, may contribute to angiogenic control before the proliferative stage. However, corticosteroid treatment can also result in cataract formation, glaucoma, and ultimately elevate blood glucose levels. In vitro studies demonstrate that PGE2 increases VEGF expression and that inhibiting PGE2 receptors with antagonists decreases the production in a dose-dependent manner[53,54]. In line, multiple experimental systems show that inhibiting PGE2 prevents or slows DR[31,55,56].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of COX and thereby the synthesis of all downstream PGs as well as VEGF, IL-6, IL-8 and other cytokines[57]. NSAID

treatment shows favorable clinical effects on inflammation and macular edema[13,40,58]. In streptozotocin-induced diabetic rats the NSAID celecoxib significantly inhibits PGE2 secretion, retinal VEGF expression and vascular leakage[38,59]. In other animal models, administration of NSAIDs (nepafenac, aspirin, meloxicam) inhibits diabetes-induced retinal microvascular disease and prevents early DR[60,61].

Growing clinical evidence confirms experimental data that inhibiting PGs pharmacologically slows progression of DR in patients[32,62,63]. It was first observed a half century ago that rheumatoid arthritis patients taking the NSAID aspirin showed reduced incidence of DR.[64] Two large multicenter clinical trials later examined this observation. The Early Treatment Diabetic Retinopathy Study (ETDRS) examined the effect of 650 mg aspirin on advanced DR65. The Dipyridamole Aspirin Microangiopathy of Diabetes (DAMAD) Study tested the impact of 990 mg aspirin in patients with early DR[66]. While patients with more advanced DR showed no benefit in ETDRS, the DAMAD study showed higher aspirin doses slowed the development of retinal microaneurysms. This latter observation is supported by a randomized 3-year pilot study where the NSAID sulindac prevented development and progression of DR[67]. Another recent prospective controlled trial, conducted by the National Eye Institute, demonstrated that the oral NSAID celecoxib significantly reduced vascular leakage in patients with DR despite early treatment stoppage due to cardiovascular toxicity concerns[68]. Finally, a recent randomized clinical trial by the Diabetic Retinopathy Clinical Research (DRCR) Network reported that intravitreal injection of a corticosteroid, triamcinolone acetonide, significantly reduced DR progression[69].

Ophthalmologists use NSAIDs extensively to treat postoperative inflammation, pain, and macular edema[33]. Of all the commercially available topical ophthalmic NSAIDs, ketorolac possesses more safety and efficacy studies than any other[13,33]. Ketorolac 0.5% (Acular) and ketorolac 0.4% (Acular LS) are older formulations with limited vitreous bioavailability.[70,71] In 2009, the Food and Drug Administration (FDA) approved a preservative-free 0.45% ketorolac formulation (Acuvail) with enhanced pharmacokinetics. Incorporation of the vehicle, carboxymethylcellulose, increases ketorolac adhesion and permeation in the eye[70,72,73]. Topical administration minimizes systemic exposure, and the potential for cardiovascular, renal and gastrointestinal toxicity associated with long-term oral application[13,74].
Regional corticosteroids have been shown in several large randomized controlled trails to be effective at treating DME, but the association between the intraocular cytokine profile and DME resolution following use of intravitreal corticosteroids have not been explored.

4.0 OBJECTIVES

This research study is being conducted for scientific purposes only.

Our current goals include confirming inflammation mediators are biomarkers of DR and DME

The Aim of this project is to measure aqueous PGE2 and inflammatory cytokines before and after treatment of DME with intravitreal corticosteroid injections.

5.0 STUDY DESIGN

Over a prior 3 year study period, we successfully enrolled 164 ***diabetic patients corresponding to stages 1, 3, and 5 (23 (12.5%) patients with no DR, 23 (12.5%) patients with PDR, and 118 (75%) patients with moderate NPDR)***, assigned according to grading of baseline fundus photographs per established criterion [97].

In cases of disease asymmetry, we examined both eyes and scored the more severe eye toward the recruitment goal. In the landmark United Kingdom Prospective Diabetes Study (UKPDS), roughly 20% of diabetic patients had retinopathy in 1 eye but not the other[98].

We also enrolled ***100*** age-matched patients without diabetes who were undergoing unilateral vitrectomy surgery for non-inflammatory conditions such as epiretinal membrane or macular hole. We removed aqueous fluid that is typically discarded and collected and stored at -80° C. Aqueous fluid will be tested for *inflammatory markers* as detailed below to provide a reference level for cross-comparison analysis.

We successfully recruited all 118 patients and over 90% of subjects have exited the study.

We want to continue to pursue this hypothesis for one more year as our initial data analysis from the original study shows a possible direct correlation between aqueous biomarkers and DME. We propose treating the DME with corticosteroid to assess the effect upon the intraocular cytokines.

5.1.1 RANDOMIZATION

Eligible patients with moderate NPDR with DME defined as central subfield thickness on Heidelberg OCT of 320 microns or higher as well as evidence of subretinal or intraretinal fluid on OCT, in at least one eye.

Patients will be sequentially randomized 1:1 to either receive Intravitreal dexamethasone 0.7mg implant or fluocinolone acetonide 0.19mg implant. These injections are standard of care and have been approved by the US FDA for this indication.

5.1.2 STUDY ASSESMENTS

All enrolled patients will undergo complete ophthalmic examination of both eyes including best corrected visual acuity, intraocular pressure (IOP) measurement, slit-lamp examination, dilated funduscopic examination, SDOCT, optical coherence tomography angiography (OCTA), color fundus photography of the retina per standard of care (SOC). HbA1c will be tested in the local lab per SOC. All patients will undergo bilateral aqueous biopsies. The tap will occur in clinic with all aseptic precautions and Dr Kim's research assistant or co-investigator will hand carry all samples back to his lab for processing and storage.

All enrolled patients will follow with Dr Kim and Dr Gangaputra per SOC every 1- 2 months for 12 months. At each follow up visit, they will undergo a full exam to evaluate for any AE's and repeat eye exam along with any clinically indicated imaging. Aqueous biopsies will be conducted every 1-2 months in both eyes.

6.0 STUDY POPULATION AND ENROLLMENT:

We will include up to 20 adult type II diabetic patients randomized 1:1 (10 per group) to receive intravitreal dexamethasone 0.7mg or fluocinolone acetonide 0.19mg implant with baseline moderate NPDR and DME

Randomization Inclusion Criteria: Adult patients age 18 years or older with type II diabetes, with baseline moderate NPDR and DME.

Exclusion Criteria: Patients with a history of previous vitrectomy in either eye; prior antivegf intravitreal injection within 3 months; co-existent non diabetic macular, retinovascular, or inflammatory disease; history of ocular trauma; aphakia; presence of an anterior chamber intraocular lens; current use of prescription systemic NSAIDs or regular use of nonprescription NSAIDs including aspirin (defined as 4 days or more a week for at least 2 weeks a month); blood pressure > 180/110 mmHg; risk for corneal melting; and inability to comply with follow-up.

7.0 STUDY PLAN

Clinical Examination

All enrolled diabetic patients will undergo complete baseline ophthalmic examination of both eyes including best corrected visual acuity, intraocular pressure (IOP) measurement, slit-lamp examination, dilated funduscopic examination, spectral-domain optical coherence tomography (OCT), color fundus photography and OCTa. Deidentified images will be read in a masked manner by Dr. Gangaputra, images will be stored on parent software (Optos, Spectralis OCT) using only the patient ID. Data from image reads will be stored on our Redcap server.

Aqueous Sample Collection

The principal investigator is a fellowship-trained vitreoretinal surgeon and uveitis specialist who routinely performs aqueous biopsies on patients for diagnostic purposes and will perform all procedures in this proposal. After topical anesthetic, antibiotic and 5% povidone-iodine application, a 30 gauge needle on a 1 ml tuberculin syringe will be inserted into the anterior chamber and used to collect 0.1 ml of aqueous fluid from each eye. Another drop of antibiotic will then be applied and the patient will be given antibiotic eye drops to apply 4 times a day for 3 days. The aqueous sample will be directly transferred via ice to storage at -80 °C for future testing.

Measurement of PG levels

The Eicosanoid Core Laboratory at Vanderbilt will use liquid chromatography electrospray ionization tandem mass spectrometry, which provides greater accuracy than ELISA testing, to analyze thawed aqueous samples for all PGs (PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2, Thromboxane A_2)[99]. Analysis of all PG classes is important because levels of other PGs such as PGI_2 (prostacyclin), a potent vasodilator, may also correlate with DR severity[100].

Measurement of Inflammatory cytokines

Due to limited volumes, a microparticle bead-based multiplex assay will be used to measure

inflammatory aqueous cytokines as previously described[21,34]. In brief, aqueous samples will be thawed and prepared using the Millipore Multiplex Human Cytokine/Chemokine Panel (Millipore Corporation, Billerica MA, USA). Bead samples will then be analyzed with flow cytometry (Bio-Plex Array Reader; Bio-Rad, Hercules, CA) for 16 cytokines: Eotaxin-1, Flt-3 ligand (Flt-3L), GRO, interferon-gamma (IFN-γ), IL-1β, IL-6, IL-8, IL-10, IL-12 (p40), IP-10, MCP-1, TNF-α, VEGF, regulated on activation normal T expressed and secreted (RANTES), PDGF-AA and PDGF-AB/BB. Stored plasma will be thawed and analyzed for the same 16 cytokines with the multiplex assay. In addition, C-reactive protein (CRP), sICAM-1, sVCAM-1, and sTNF-R1 levels will be analyzed using liquid chromatography electrospray ionization tandem mass spectrometry. CD14 levels will be analyzed using ELISA

Adverse Events
All patients will be reexamined 30 minutes post biopsy for vision, bleeding, hypotony and cornea integrity. They will also be questioned about any level of discomfort. We will contact each patient by phone 1 day after aqueous sampling and inquire about changes in vision or pain. We will instruct patients regarding warning signs and provide a direct number to call if they are experiencing unusual or persisting symptoms. A safety committee will monitor any adverse events.

Potential Pitfalls and Alternative Strategies
We have already overcome major potential procedural challenges. Needle withdraw is difficult in some patients. Consequently, proficiency and first-hand experience with this technology is required. The principal investigator routinely performs aqueous biopsies on patients and will perform all procedures in this proposal.
There have been no adverse events reported thus far. The most common side effect is subconjunctival hemorrhage secondary to anesthesia.

We also have considerable experience testing aqueous samples for cytokines using a microparticle bead-based multiplex assay that allows small volume (50 µl) testing of multiple cytokines[21,34]. Aqueous fluid is an accurate means to test intraocular inflammatory mediators and can be repeated serially; however, biopsies are limited by small sample volumes (100 µl), which prevent “second chances” or repeat testing. We will also analyze blood samples for inflammatory mediators. Establishing correlations between intraocular inflammatory mediators and serum levels would mitigate biopsy complications by allowing for independent serum analysis.

The Vanderbilt Eye Institute (VEI) is a modern facility opened in 2008 with all the necessary staff, imaging equipment, and procedure rooms to obtain blood and aqueous specimens safely. The VEI has a fully staffed clinical trials division, Lindsay Veach and Havin Abdulkadir Clinical Trials Specialists, who will oversee this operation and help address any logistical problems as they arise. The VEI also provides an ample population in which to recruit, with an estimated 15,000 diabetic patient visits per year.

Establishing that the level of PGE_2 directly associates with DME is our primary benchmark for success. Other secondary benchmarks include: 1) elevated cytokines (VEGF, IL-6, and IL-8) 2) predicting disease progression and/or complications over time with inflammatory mediator levels

8.0 PROTOCOL DEVIATIONS

Protocol deviations will be recorded and reported to the local IRB in a timely manner. If the protocol deviation placed the participant at increased risk, it will be reported by the Principal Investigator and the IRB by the next business day. If the protocol deviation resulted in no increased risk, the event will be reported to the IRB at continuing review.

9.0 ADVERSE EVENTS

Aqueous biopsies are performed routinely and are generally considered minor procedures. Risk of bleeding and infection are rare. The principal investigator is well experienced in this procedure having performed nearly 1000 of them in the standard care of patients with retinal disease and ocular inflammation. Careful assessment of each patient will be done after each biopsy to evaluate for complications and ensure patient safety. All topical NSAIDS used in this study have been administered to millions of patients with excellent overall safety. This greatly improves the safety of this study since it employs drugs that are approved for ophthalmic use and have well-established track records.

Investigators will determine at periodic intervals if any clinical adverse experiences occur during the period from enrollment until after study drug termination. A safety monitoring committee will also be established to independently review complications. Most data normally collected as part of a clinical study to guarantee patient safety and determine efficacy is obtained as part of normal clinical care of patients in the eye clinic at Vanderbilt Eye Institute. Examples include: visual acuity, intraocular pressure, corneal and retina findings. All available clinical data, exam findings, and clinical impressions from the primary team, will be monitored for adverse events. The investigator will evaluate any changes in laboratory values and physical signs and will determine if the change is clinically important and different from what is expected in the course of treatment of patients with diabetic retinopathy. If clinically important and unexpected adverse experiences occur, they will be recorded on the adverse event case report form. Investigators will report all serious and unexpected adverse events to the Principal Investigator and the local IRB in a timely manner. All adverse events that are deemed non-serious and or not unexpected will be reported to the IRB annually at continuing review.

Patients will all be closely monitored in a clinic setting, particularly after any intervention. This will allow for prompt treatment of any suspected adverse events, including allergic reactions, infection, bleeding, visual acuity changes, retinal or corneal changes, and intraocular pressure changes. In the case of an adverse event that is suspected to be related to study drug material, the Principal Investigator will be notified and evaluate the situation. The study drug will be held until the event is evaluated and a decision will be made on an individual basis whether the drug will be restarted or permanently discontinued.

9.1 ADVERSE EVENTS

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An adverse event therefore can be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease

temporally associated with the use of an investigational product, whether or not the incident is considered to be related to the investigational product. Incidences of adverse reactions will be systematically collected and will be considered adverse events.

A serious adverse event (SAE) is defined as any untoward medical occurrence that meets all the following criteria:

a. Results in death
b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
c. Requires inpatient hospitalization
d. Prolongs an existing hospitalization
e. Results in persistent or significant disability or incapacity
f. Results in a congenital anomaly or birth defect
g. Important medical event that requires an intervention to prevent any of a-f above.

9.2 ADVERSE EVENT COLLECTION PERIOD

Collection of adverse events will commence from the time that the participant is first administered the study corticosteroid injection. Routine collection of adverse events will continue until the event is resolved. Any adverse events spontaneously reported to the investigator or observed by the investigator will also be collected and recorded.

9.3 ADVERSE EVENT REPORTING

Any adverse effects will be immediately reported to the IRB and the study will be stopped until further notice.

10.1 ETHICAL CONDUCT OF THE TRIAL

This study will be conducted with the highest respect for individual participants according to the protocol, the World Medical Association Declaration of Helsinki, the Guideline for Good Clinical Practice, and the Belmont Report. Furthermore, the study will be conducted in accordance with the Common Rule (45 CFR 46), as guided by the Department of Health and Human Services via the Office of Human Research Protections.

10.2 INSTITUTIONAL REVIEW BOARD

The investigator will submit all relevant documents to the IRB for the protocol's review and approval. The study protocol, informed consent form, and any proposed advertising or recruitment materials must be approved by the local IRB prior to any changes to the study. Written approval by the IRB of the protocol and participant informed consent document must be obtained prior to re-enrollment of any participants. If any member of the IRB has direct

participation in this trial, he or she must refrain from any IRB discussions or votes pertaining to this study.

10.3 PARTICIPANT INFORMATION, INFORMED CONSENT, AUTHORIZATION

All consent for participation in this study must occur via written consent documents, which should contain the elements of informed consent as required by 45 CFR 46 and the Declaration of Helsinki. The informed consent document will describe the planned and permitted uses, transfers and disclosures of the participant's personal and personal health information for purposes of conducting the study.

The investigator is responsible for the preparation, content, and submission to the IRB approval of the informed consent form. The informed consent form and any participant information sheet must be approved by the IRB prior to use.

The participant, or his or her legally authorized representative, must be presented with an informed consent document written in their native language and given ample opportunity to: 1) inquire about details of the study, and 2) decide whether or not to participate in the study. If the participant or legally authorized representative agrees to participate in the study, the informed consent form must be signed and dated by the participant or legally authorized representative prior to the participant being enrolled in the study. The investigator must document the date the ICF is signed in the participant's medical record. The investigator must also sign and date the informed consent form at the time of consent and prior to the participant being entered into the study. In the event that a participant is visually impaired to the point where they are unable to read the consent on their own the consent will be read to them in the presence of an impartial witness. The same time and question period will be afforded to them in order that they may fully comprehend the purposes, procedures, and potential risks of the study and of their rights as research participants. The impartial witness will also be required to sign and date the consent form.

Once signed by the participant, investigator, and impartial witness if needed, a copy of the informed consent document will be given to the participant (or legally authorized representative). The original informed consent document will be stored in the investigator's site file.

All revised informed consent forms must be reviewed and signed in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the participant's medical record and the participant should receive a copy of the revised ICF.

10.4 DATA AND SAFETY MONITORING

Dr. Kim, the Principal Investigator, will be responsible for overseeing this trial on a daily basis. He will review laboratory and clinical data daily looking for adverse events. In addition, he is available at any time for questions from the research staff. The Principal Investigator is an experienced clinician clinical investigator in diabetic patients and has experience monitoring clinical trials in such patients as either a member of a DSMB and/or principal investigator on such trials. Given the repeated need for bilateral aqueous biopsies, a safety monitoring

committee with be established to independently review complications and adverse events. Strict definitions of adverse events have been established as a priority and the Principal Investigator will review each case that meets the definition of an adverse event. In addition, the Principal Investigator will also be available to review serious adverse events in a timely manner. The Principal Investigator will be available for rapid access by the investigators in the case of the need to evaluate serious adverse events or any other major unanticipated or safety related issues. Furthermore, in cases of serious adverse events or significant findings, the Principal Investigator will unblind the treatment arm. The Principal Investigator will have the ability to pause the trial to investigate possible safety issues and/or suggest changes to the design of the study to abrogate any safety issues, including discontinuation of the study drug should it result in unacceptable adverse event.

DSMB BOARD

The DSMB board will meet after 6 months of recruitment to review the numbers of patients recruited and the baseline data will be evaluated. It is open label and the PI is privy to the randomized drug. The image reader, Dr Gangaputra is masked to the patients eye exam and study drug. The DSMB board will meet annually thereafter to review adverse events and monitoring of study conduct and design.

Potential Risks: Since this is a continuation study, there are minimal risks of unforeseen side effects and adverse events However, these risks are ameliorated by the choice of study drug which is approved for ophthalmic use, commercially available, and has been used safely for years in millions of patients. There is risk of corticosteroid injections such as cataract and glaucoma, however these FDA approved medications are very beneficial to control of DME and improved visual acuity for the pateints.

10.6 ALTERNATE TREATMENTS

The alternative treatment for DME would be regular anti-VEGF injections which are approved by FDA but require frequent administration and continuous use.

10.7 POTENTIAL BENEFITS

Patients may benefit from delay or prevention of complications of diabetes which result in severe vision loss (i.e. diabetic macular edema, vitreous hemorrhage, tractional retinal detachment).

10.8 IMPORTANCE OF KNOWLEDGE TO BE GAINED

THIS STUDY HAS THE POTENTIAL TO TRANSLATE IMMEDIATELY INTO CLINICAL CARE BY PROVIDING A NEW MEANS TO PREVENT PROGRESSION OF DIABETIC MACULAR EDEMA AND VISION LOSS. THE INFORMATION GAINED FROM THIS STUDY WOULD BE INSTRUMENTAL IN DESIGNING A PHASE III MULTICENTER STUDY TO FURTHER INVESTIGATE THE THERAPEUTIC EFFICACY OF INTRAVITREAL CORTICOSTEROIDS FOR THE PREVENTION OF DIABETIC-RELATED VISION LOSS.

11.0 DATA HANDLING AND RECORDKEEPING

11.1 SOURCES OF RESEARCH MATERIAL

All materials will be collected and recorded for research purposes. The data collected during this investigation will be obtained from the medical record. The patients will have samples collected for specialized laboratory analyses.

11.2 PARTICIPANT CONFIDENTIALITY

The investigators and Vanderbilt Health affirm and uphold the principle of the participant's right to protection against invasion of privacy. Throughout this study, a participant's source data will only be linked to the clinical study database or documentation via a unique study identification number. As permitted per HIPAA regulations, limited participant attributes such as sex, age, or gender may be used to verify the accuracy of the participant's unique identification number. Copies of any participant source documents provided to entities outside of Vanderbilt University Medical Center (including the FDA, IRB, or NIH) will have all personally identifiable information removed (eg, participant name, address, date of birth, etc.)

The research coordinators, principal investigator, or co-investigators will collect data and record it on case report forms designed specifically for the study. The data will then be entered in a password protected, privacy-secured, computerized database. The data collection forms will be kept in a locked cabinet in a locked office. Only the study investigators and study coordinators will have access to the locked cabinet. All samples obtained for this study will be assigned a code which will not identify the subject. The only key to the code will be in the password-protected computer database. Dr. Kim will be responsible for maintaining confidentiality of data and codes. Only study investigators and the study coordinators will have access to the code and information that identifies a participant as a being in this study. The results of analyses run on those samples will not be reported to the participant or study team member. No one else, including relatives, doctors, employers or insurance companies will be allowed to view the test results. The codes linking the patients with their data will be destroyed after all participants have completed the study and the data has been through quality assurance processes. Once the code is destroyed, there will be no way to trace the data or samples back to the participant. The reason for not destroying the code earlier is to ensure quality assurance and that the data is complete and accurate. Informed consent documents will not bear the study identification number so that once the code is destroyed; there will be no possible way the results could be traced back to the individual.

All patients will provide consent for the intravitreal injections which are separate from the consent forms for the study. Consent forms will be filed and stored.

11.3 RECORD RETENTION

The investigator will keep all study-specific documents, an identification log of all participating patients, source worksheets, original signed and dated informed consent documents, and copies of all CRFs in a locked and secure office or storage space until at least three years after the completion of the study.

12.0 COMPENSATION

The study will provide $25 dollar gift cards to patients to cover their travel cost. Patients will receive a $50 gift card to compensate for the longer appointment times, or longer travel times. The study will provide compensation to cover the cost for co-pays.

13.0 COMPENSATION AND TREATMENT FOR INJURY

If it is determined by Vanderbilt and the Principal Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then the patient and/or patient's insurance will not have to pay for the cost of immediate medical care provided at Vanderbilt to treat the injury.

There are no plans for Vanderbilt or the Principal Investigator to pay for any injury caused by the usual care patients would normally receive for treating their illness or the costs of any additional care. There are no plans for Vanderbilt or the Principal Investigator to give money for any injury.

14.0 References

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