Title

Bevacizumab against recurrent retinal detachment (BEARRD)

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Project Summary

Rhegmatogenous retinal detachment (RD) is a serious vision threatening condition. Pars plana vitrectomy (PPV) is the most common and successful surgical procedure to repair

rhegmatogenous RD. With the introduction of small-gauge (23 and 25 gauge) PPV, the success of PPV for rhegmatogenous RD has improved to nearly 87% with only one surgical procedure[1,2]. In the remaining 13%, however, PPV failure causes poor visual outcomes, averaging 20/100 visual acuity[1]. The primary reason for primary PPV failure is proliferative vitreoretinopathy (PVR)[3]. PVR develops when retinal and subretinal cells are released into the vitreous after a retinal break[3]. The vitreous, which is rich in growth factors, promotes proliferation and fibrosis of these retinal cells, leading to tractional and/or recurrent rhegmatogenous RD[3]. Unfortunately, recent pharmacologic attempts to prevent PVR development in clinical trials have failed[1,4,5]. Interestingly, inhibition of vascular endothelial growth factor (VEGF) signaling prevents PVR progression and recurrent RD in experimental animal models[6]. This finding led us to hypothesize that bevacizumab, a ubiquitously used and safe anti-VEGF medication used intraocularly, could be a potential therapeutic prophylaxis against PVR and recurrent RD.

The primary goal of this study will be to determine if intra-operatively administered bevacizumab can reduce the incidence of recurrent RD and PVR. During routine PPV repair of rhegmatogenous RD, a single dose of bevacizumab will be administered through the trocar at the end of surgery. This method of administration has the advantage of eliminating any risk of intraocular injection, including the risks of RD, infection, and lens damage. The only risk of this study is that of the medication itself, which has been shown to be safe in a large prospective randomized clinical trial[7] and is now widely used as first line treatment for exudative macular degeneration, diabetic macular edema, and retinal vein occlusions. Our study will begin with a retrospective review of our current surgical practice to determine our institution's success rate for primary PPV to repair retinal detachment. Success will be defined as one PPV to repair RD after 6 months follow up, and failure will be stratified by cause with specific attention directed toward PVR. We intend to query the most recent 4-6 years to identify a control group of approximately 400 patients, all receiving PPV. We then intend to enroll patients into the study over a one-year period, estimating enrollment of approximately 100 patients in this prospective cohort study. We will follow patients for 6 months post-operatively, primarily including visual acuity and ophthalmoscopy to determine incidence of recurrent RD and PVR.

This proof-of-concept study will address whether anti-VEGF therapy can reduce the incidence of recurrent RD and PVR. Should this study be positive, a larger prospective randomized clinical trial can be explored to confirm our findings and possibly establish anti-VEGF therapy in the peri-operative period as the gold standard prophylaxis against PVR. Future considerations will address whether additional anti-VEGF injections in the post-operative period can further reduce the incidence of PVR.

Background and Significance

Rhegmatogenous RD is an important cause of severe vision loss, occurring in approximately 10.5 per 100,000 patients annually[8]. A rhegmatogenous RD develops after a break in the retina allows liquefied vitreous to enter the sub-retinal space and dissect the retina from the retinal pigment epithelium (RPE) and choroid. Recent advances in small-gauge vitrectomy technology have greatly improved anatomical success rates and visual outcomes. Briefly, the vitreous gel is removed from the vitreous cavity, the subretinal fluid is drained thereby flattening the retina, adhesions are created between the retina and RPE with laser, and the vitreous cavity is filled with

long acting gas to tamponade the retina against the RPE. In two independent studies of primary PPV for rhegmatogenous RD, 87% of patients have complete success and require no additional retinal operations[1,2]. In those patients requiring no further surgery, final median visual acuity is approximately 20/40[1]. However, in the group of patients who require further retinal surgeries, final median visual acuity significantly decreases to worse than 20/100[1]. The primary cause for surgical failure and worsened visual acuity is PVR.

PVR develops in 5–10% of patients after rhegmatogenous RD[1,3]. PVR begins when retinal and sub-retinal cells are liberated into the vitreous gel after a retinal break. The most common cells found in PVR membranes are retinal glial cells, RPE cells, fibroblasts, and inflammatory cell types[3]. The vitreous gel contains a multitude of growth factors and it is hypothesized that exposure of these cell types to vitreous causes proliferation of glial and RPE cells, and differentiation of RPE cells to fibroblasts and myofibroblasts[3]. These cell types adhere to the retina and form contractile epi-retinal membranes that open old retinal breaks or create new retinal breaks, causing tractional and recurrent rhegmatogenous RD. PVR-associated recurrent RDs are then treated surgically with a combination of secondary and thorough PPV, scleral buckling, membrane peeling of PVR membranes, and/or long-term tamponade with silicone oil. Although anatomic success rates are high, with up to 90% success with one additional surgery and 99% success after multiple surgeries, visual acuity outcomes are poor with median final visual acuity of less than 20/100[1,3]. These results demonstrate the need for effective prophylaxis against PVR.

Despite our knowledge of the pathophysiology of PVR, no clinical trials have identified any useful prophylactic pharmaceutical agents against PVR. Based upon the model of RPE and retinal glial cell proliferation in the pathogenesis of PVR, agents such as 5-fluorouracil[1,9] (5-FU) and daunorubicin[5] have been studied as prophylactic agents to prevent PVR and recurrent RD. In patients with known PVR, daunorubicin did not improve surgical outcomes or final visual acuity[5]. In patients at high risk for PVR development, 5-FU in combination with low molecular weight heparin (LMWH) did reduce PVR and decrease the number of retinal operations[9]. However, 5-FU and LMWH as an adjunctive therapy in primary PPV for all comers had no effect upon PVR, retinal surgeries, or final visual acuity[1]. Finally, triamcinolone was investigated to reduce PVR via its anti-inflammatory properties, but in conjunction with PPV, membrane peeling, and silicone oil tamponade for PVR-associated RD, triamcinolone had no effect upon retinal re-attachment, PVR, or visual acuity[4]. Thus, there is no effective prophylaxis against PVR and further investigation is warranted.

As discussed earlier, the current pathophysiologic model is that the vitreous gel is rich in cytokines and growth factors that drive PVR. It is hypothesized that molecules like platelet-derived growth factor (PDGF) stimulate proliferation of RPE and glial cells, while transforming growth factor β (TGF-β) and connective tissue growth factor (CTGF) promote fibrosis[3]. Many studies have focused on PDGF and its receptors as key early steps in the pathogenesis of PVR. Activation of the PDGF receptor α (PDGFRα) increases PVR, and inhibition of PDGFRα reduces PVR in a rabbit model[10-12]. This pro-PVR effect, however, is not driven by PDGF but instead stimulated by non-PDGF growth factors that indirectly activate PDGFRα[13,14]. Interestingly, VEGF inhibits PDGF-driven direct PDGFRα activation and increases non-PDGF indirect PDGFRα stimulation[15]. This finding led to the hypothesis that VEGF functions as a key

switch that determines if PDGFRα is stimulated by PDGF or non-PDGF ligands, which activate PVR. Thus, VEGF promotes PVR by inhibiting its inhibitor. Confirming this hypothesis, ranibizumab, a VEGF antagonist, reduces non-PDGF-stimulated PDGFRα activation and decreases experimental PVR in a rabbit model[6]. Therefore, ranibizumab is a potential therapeutic to prevent PVR by modulating PDGFRα signaling.

Ranibizumab is a safe and effective therapeutic for the treatment of exudative age-related macular degeneration (AMD), diabetic macular edema, and central retinal vein occlusion. Ranibizumab was first approved for the treatment of classic and occult choroidal neovascularization in exudative AMD[16,17]. The safety profile of ranibizumab is excellent with no increased systemic adverse events and a very low risk (0.05%) of local infection. Bevacizumab is a second anti-VEGF agent that costs up to 40-fold less than ranibizumab. Off label usage of bevacizumab led to the Comparison of AMD Treatments Trial (CATT), which investigated the efficacy and safety of intra-vitreal bevacizumab injection. The CATT trial found that ranibizumab and bevacizumab were equally efficacious with equally few systemic and local adverse events[7]. Based upon this trial, bevacizumab is now first line standard of care treatment for exudative AMD and additionally for diabetic macular edema and retinal vein occlusions.

Risks associated with intravitreal administration of bevacizumab as seen in the CATT trial are endophthalmitis, retinal detachment, and cataract. The risk of retinal detachment and cataract occur because a needle is used to penetrate the pars plana to administer the drug. In this study, bevacizumab will be delivered via the previously placed surgical cannula, thereby eliminating the risk of retinal detachment and cataract from the drug administration. Endophthalmitis is a risk factor for any eye surgery.

Since bevacizumab is a safe and useful anti-VEGF agent, we hypothesize that bevacizumab could reduce PVR. We plan to investigate if bevacizumab can be used as a prophylactic agent against PVR by providing a one-time dose of bevacizumab intra-operatively. Bevacizumab (1.25 mg/0.05 mL) will be administered at the end of primary vitrectomy surgery for rhegmatogenous RD. This potential prophylactic is known to be incredibly safe with very low patient risk and could potentially be the first biologic prophylaxis against PVR.

Specific Aims/Study Objectives

Purpose

To investigate if intravitreal bevacizumab injection during primary vitrectomy surgery can reduce recurrent RD and PVR.

Duration

The study will last 6 months for each subject. In prior studies of recurrent RD after primary RD repair[1], 6 months is the typical end point used and most recurrent RD occurs between 6 weeks and 3 months. We plan to enroll every patient with rhegmatogenous RD that qualifies for a primary vitrectomy RD repair surgery. We plan to enroll patients over 1 year, estimating approximately 100 enrolled patients. These 100 patients will be compared to retrospective

historical data from 400 patients who underwent retinal detachment surgery at UW Hospital over the last 4-6 years. The data analysis will be performed at the end of the study. It is expected that the study will be completed and the results will be available within 18 months from time of commencement.

Outcome measures

Primary: Complete success of primary vitrectomy surgery, defined as retinal re-attachment without the need for any additional surgical procedures.
Secondary: Visual acuity and presence of PVR.

Research Design and Methods

Recruitment and Location

Subjects are patients with a rhegmatogenous RD who are under the care of one of the ophthalmologists at University of Wisconsin Hospital and Clinics (UWHC). Ophthalmologists involved in the patients' clinical care will be the first to approach patients about the study. For patients who are interested and meet the criteria, the treating ophthalmologist will explain the study, guide the patient through the study specific consent form, and answer subject questions.

Subjects

Subject population

The study population will consist of approximately 100 eyes of patients recruited by ophthalmologists at UWHC.

- Inclusion criteria
    - Age ≥ 18 years
    - Eyes with rhegmatogenous retinal detachment
- Exclusion criteria
    - Presence of PVR
    - Need for a procedure other than primary PPV such as a scleral buckle with or without PPV, laser retinopexy, or pneumatic retinopexy.
    - Recent intravitreal injection of an anti-VEGF agent less than 3 months prior
    - Secondary retinal detachment repair
    - Use of silicone oil as tamponade agent
    - Patients less than 18 years of age
    - Pregnancy
    - Known previous adverse response or contraindication to intravitreal bevacizumab
    - History of stroke or malignant hypertension in the previous 6 months

Consent procedures

The patients will be assessed by the treating physician for eligibility for the study. The results of a standard care dilated funduscopic exam, done for clinical purposes, will be used to determine research eligibility. For the patients who qualify for the study, the treating physician will explain

the study to them, including the risks. The subjects will have the opportunity to ask questions. They will receive a copy of the consent form. Patients who agree will then be asked to sign the consent form. Patients may be able to take the consent form home prior to signing for further consultation if desired. Women of childbearing age who are unsure of their pregnancy status will be excluded from the study unless they first undergo a pregnancy test.

Research Design

1. This is a prospective case series of approximately 100 eyes with rhegmatogenous RD over a one-year duration. These patients will be compared to a historical population of 400 patients who underwent retinal detachment surgery at UW Hospital over the last 4-6 years. Previous studies estimate an approximately 86.7% complete success rate for primary vitrectomy. Because each surgeon has different rates, we will compare our prospective 100 cases to our own internal controls. We will begin the study with a retrospective review of our own success rates. In order to determine the primary success rate, we will query Healthlink for 400 records from between September 2, 2009 and September 2, 2014 of patients receiving PPV surgery. We will define this as retinal re-attachment without the need for subsequent retinal surgical procedures during a 6-month follow up duration. We will also stratify our failures into categories, including PVR, new primary retinal break, and other. We will identify a stable rate of primary PPV success in our control group to ensure that no trend toward improvement over time exists.

2. Patients identified as candidates who express interest in participating will sign a consent form and will clinically undergo standard care primary PPV surgery for retinal re-attachment.

3. PPV will be performed in the typical manner with initial core vitrectomy, followed by peripheral vitrectomy. Air fluid exchange will be performed and the sub-retinal fluid drained. Once the retina is flat, endolaser will be applied as appropriate for closure of retinal breaks. After laser retinopexy and prior to air-gas exchange, intravitreal bevacizumab will be administered through a cannula. Either perfluoropropane (C3F8) or sulfur hexafluoride (SF6) gas will then be administered for long-term retinal tamponade and the vitrectomy ports closed in the usual manner. Studies have shown no adverse effects from bevacizumab when used in a gas-filled eye.[19, 20] The administration of bevacizumab is the only part of the surgery that will differ from the standard of care.

4. All patients will be subsequently examined at 1 day, 1 week, and 1 month post-operatively in the usual manner. Patient's intraocular pressure and visual acuity will be measured at these visits. Study activities will take place at the standard care visits that happen 3 months and 6 months postoperatively, within a one-month window. The following clinical data will be collected from these visits for the study: visual acuity, intraocular pressure, presence and grade of PVR, and attachment of the retina. Grading of PVR will be based on the updated Retina Society classification[18], but modified for simplicity. Grade A is defined as pigment clumps, Grade B is defined as wrinkling on the retinal surface, and Grade C is defined as full-thickness rigid retinal folds (e.g. star fold).

Data and Safety Monitoring Plan

The only risk of this study involves the intraocular drug bevacizumab. Bevacizumab will be delivered via the previously placed cannula so there will no be no risk associated with the method of intraocular injection. Patients who have a known previous adverse response to bevacizumab will be excluded from the study.

The CATT trial demonstrated the safety of intra-ocular bevacizumab in 1200 patients[7]. The CATT trial found a 2-3% risk of arterial thromboembolic events, <1% risk of worsening hypertension, 1% risk of venous thromboembolic events, and 20% risk of hospitalization of any cause[7]. All of these events were equal to the control group and general population, after being adjusted for age and overall risk factors[7]. Nevertheless, we will use a questionnaire, similar to the CATT trial, which monitors for the above events at the 3-month and 6-month visit. The questionnaire will ask:

1. Since your surgery or most recent BEARRD visit, have you had any hospitalizations?
2. Since your surgery or most recent BEARRD visit, have you any heart attacks or strokes?
3. Since your surgery or most recent BEARRD visit, have you had any blood clots?
4. Since your surgery or most recent BEARRD visit, have you had any episodes of uncontrolled blood pressure requiring hospitalization or emergency room care?

Since we are mostly investigating rare events in a small study population, the results of this questionnaire will be analyzed after 50 patients to determine if bevacizumab caused any increased risk to the study population. For such a small study, the principal investigator will be responsible for monitoring the safety data. Since there is no control study population, the event rates in the CATT trial will be used as the control group. For hypertension, arterial thromboembolic events, and venous thromboembolic events, the expected rate is a low 1-2 events among 50 people, requiring 9 events for any group to reach statistically significance that would warrant stopping the study using Fisher's exact test. For hospitalizations, 20 events would be needed to meet statistical significance to stop the study using the same methodology. The data will be analyzed after 50 patients complete their 3-month visit, again after 50 patients complete their 6-month visit, and at study conclusion. The study will be stopped if the above criteria are met. After 50 patients complete their 6-month visit and at study conclusion, the safety data will be reviewed, and the results will be communicated to the IRB. Patients who withdraw prematurely will be included for analysis of treatment effect if there are adequate data points for analysis.

It is unknown whether bevacizumab poses a risk to pregnant females or fetuses. Therefore, any woman of childbearing age who is unsure of her pregnancy status will be excluded from the study unless she first undergoes a pregnancy test. A urine pregnancy test will be provided at no charge to the patient. Women who are of childbearing age and are sexually active will need to be on birth control for three months after receiving the study medication. Abstinence is an acceptable form of birth control.

Potential risks

The potential risks related to study participation include:

1. Increased inflammation and endophthalmitis. Although extremely rare, it is possible to have an increase in inflammation and even endophthalmitis from bevacizumab.

2. Large, controlled trials and meta-analyses have been done looking at adverse events from bevacizumab. These have shown that “anti-VEGF monoclonal antibodies did not significantly increase overall mortality, cardiovascular mortality, stroke, myocardial infarction, VTEs, or hypertension. While the informational drug brochure for bevacizuamb states arterial thromboembolic events, hypertension, gastrointestinal perforation, and hemorrhage have have been reported from unapproved intravitreal use, these events are “reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”
3. Confidentiality breach

Protection of subjects

Patients will be examined at study enrollment and at post-operative visits including 1 day, 1 week, 1 month, 3 months, and 6 months as would be done regardless of the study. The visits will include a standard ophthalmologic examination including visual acuity, intraocular pressures, and slit lamp biomicroscopy. All complications will be recorded. Patients will be instructed to call immediately for an appointment if they notice any standard care surgery risks such as a change in the vision, appearance of the eye, or development of pain in the eye. Data collection forms will include the study identification number; no names will be used in the forms. Presentations and publications will not identify individual patients.

Statistical Considerations

A Chi-square test will be used to compare percentage success of primary vitrectomy for retinal detachment with bevacizumab to our internal control standard over the last 4-6 years. Based upon power calculations, we estimate a roughly 15% percent failure rate in our current practice. With a goal of a 60% reduction in failure rate, 100 prospective subjects versus about 400 control subjects will provide a power of 80% at the standard α error of 5%. A Chi-square test will also be used to compare the percentage of patients with PVR in our prospective case series versus our control population. Unpaired t tests will be performed to compare visual acuity (VA) and intraocular pressure.

Data and Record Keeping

Research intervention will be conducted in a private room; collection of sensitive information about subjects will be limited to the amount necessary to achieve the aims of the research. Data collection forms will include the name code and study identification number; no names will be used in the forms. Presentations and publications will not identify individual patients.

All paper data will be stored in locked cabinets. All the electronic data will be stored in password-protected computers. This will be kept at UWHC sites in a room with number lock available only to individuals listed in study protocol. The confidentiality of records will be maintained in accordance with applicable state and federal laws. All the identifiers and information in paper format will be shredded. The electronic data will be deleted at the conclusion of study.

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