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Proof of Concept Study of the Effectiveness of Ozurdex in lieu of Oral Corticosteroids for the Control of Active Intermediate and Posterior Uveitis Requiring Immunosuppressive Drug Therapy

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JHM IRB - eForm A – Protocol

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1. **Abstract** (Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.) See background.

2. **Objectives:**

This is a single arm proof of concept study evaluating whether or not the dexamethasone pellet (Ozurdex®, Allergan, Irvine, CA) can replace oral corticosteroid (e.g. prednisone) in the treatment of active sight-threatening, noninfectious intermediate or posterior uveitis in which immunosuppressive drug therapy is indicated.

3. **Background:** Intermediate and posterior uveitis are thought to be severe intraocular inflammation that may lead to permanent visual loss. It is estimated that these forms of uveitis comprise the fifth or sixth leading cause of blindness and tend to affect working class age patients, thus causing loss of work hours and diminished productivity and quality of life. Because the posterior segment of the eye is not adequately treated by corticosteroid drops often systemic drug therapy is used including oral corticosteroids or prednisone. Prednisone can have a myriad of side effects in approximately onequarter to one-third of cases treated in tertiary care centers such as ours, additional medications such as immunosuppressive drugs are required to control the disease and/or to allow for appropriate tapering of oral prednisone to subsequent levels that have a low side effect profile when delivered over a long period of time. Typically, chronic prednisone therapy in doses of 7.5 mg daily or less are thought to have a low enough side effect profile to be amenable to long-term therapy. However frequently immunosuppressive drugs are required to get the dosing to this level. There are occasions when patients are intolerant of any dose of oral corticosteroids or are intolerant of the higher doses of oral corticosteroids (30 – 60 mg daily) and therefore this treatment modality is avoided due to prednisone's attendant side effects. Although periocular and intravitreal corticosteroids injections may be performed, with these modalities the standard of care is to wait until the disease reactivates before instituting such therapy and therefore a chronic suppressive dose is not obtained. The fluocinolone acetonide implant (Retisert®, Bausch and Lomb, Tampa, FL) is FDA-approved for the treatment of intermediate and posterior uveitis and it is equally effective in controlling uveitis as highdose oral corticosteroids but avoids the systemic side effects associated with the use of high doses of oral corticosteroids. However, this form of local therapy has high rates of ocular side effects, including ocular hypertension causing glaucoma and/or requiring glaucoma surgery and cataracts. Furthermore, every two and half to three years the implant is exhausted of corticosteroid and therefore repeat surgical insertion of another implant may be required. A useful potential therapy for the treatment of these patients would be a shorter-acting local corticosteroid that could be delivered in conjunction with systemic immunosuppressive drug therapy that would have a lower ocular side effect profile but still would be effective enough to replace the use of high-dose systemic corticosteroids in the treatment of active intermediate or posterior uveitis. It is possible that the dexamethasone pellet could fill this unique role in the treatment of uveitis. We propose this proof of concept study to evaluate dexamethasone pellet for this specific use among patients with active intermediate and posterior uveitis.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures
(Distinguish research procedures from those that are part of routine care): -
Single arm proof of concept interventional study.

Specifics of each clinical visit including data collected and procedures performed are as follows:

- **Baseline examination data collection consists of:**
    - Signed informed consent obtained
    - Demographic data (age, gender, race, duration of uveitis, anatomic location of uveitis, smoking status, presence of systemic disease associated with uveitis)
    - Treatment history (current therapies for the treatment of uveitis, history of corticosteroid use including periocular corticosteroids, history of immunosuppressive drug use, need for IOP-lowering medications)
    - Past ocular history (any complications due to uveitis, any ocular surgeries or procedures, presence of amblyopia, history of glaucoma or ocular hypertension, treatment to lower intraocular pressure including laser procedures and/or surgeries
    - Ophthalmic examination including best-corrected visual acuity, IOP measurement, presence and degree of uveitis activity, presence of ocular complications including cystoid macular edema (CME), findings of slit lamp examination including presence and degree of cataract, findings of fundoscopic examination including cup to disc ratio.
    - Visual field assessment
    - Slit lamp photos to assess cataract if eye(s) are phakic ○ Optic nerve photos
    - Results of baseline OCT and fluorescein angiography testing if clinically indicated ○ NEI VFQ and EuroQol administered
- Dexamethasone pellet placement occurs within 14 days of baseline examination; for patients with bilaterally active uveitis, placement of a dexamethasone pellet in the second eye should occur within 14 days of the first implantation or within 30 day of the baseline examination.
    - Adverse events related to the procedure will be collected (e.g., vitreous hemorrhage, elevated IOP, retinal detachment) at time of placement
- **1-month examination** ○ Interval treatment history (current therapies for the treatment of uveitis, history of corticosteroid use including periocular corticosteroids, history of immunosuppressive drug use, need for IOP-lowering medications)
    - Interval ocular history (any complications due to uveitis, any ocular surgeries or procedures, history of glaucoma or ocular hypertension, treatment to lower intraocular pressure including laser procedures and/or surgeries
    - Ophthalmic examination including best-corrected visual acuity, IOP measurement, presence and degree of uveitis activity, presence of ocular complications including cystoid macular edema (CME), findings of slit lamp examination including presence and degree of cataract, findings of fundoscopic examination including cup to disc ratio.
    - Results of OCT and fluorescein angiography testing if clinically indicated ○ NEI-VFQ and EuroQoL administered.
    - Adverse event reporting
- **2-month examination** ○ Interval treatment history (current therapies for the treatment of uveitis, history of corticosteroid use including periocular corticosteroids, history of immunosuppressive drug use, need for IOP-lowering medications)
    - Interval ocular history (any complications due to uveitis, any ocular surgeries or procedures, history of glaucoma or ocular hypertension, treatment to lower intraocular pressure including laser procedures and/or surgeries

- Ophthalmic examination including best-corrected visual acuity, IOP measurement, presence and degree of uveitis activity, presence of ocular complications including cystoid macular edema (CME), findings of slit lamp examination including presence and degree of cataract, findings of fundoscopic examination including cup to disc ratio.
- Results of OCT and fluorescein angiography testing if clinically indicated ○ NEI-VFQ and EuroQoL administered.
- Adverse event reporting

- **3-month examination** ○ Interval treatment history (current therapies for the treatment of uveitis, history of corticosteroid use including periocular corticosteroids, history of immunosuppressive drug use, need for IOP-lowering medications)
  - Interval ocular history (any complications due to uveitis, any ocular surgeries or procedures, history of glaucoma or ocular hypertension, treatment to lower intraocular pressure including laser procedures and/or surgeries
  - Ophthalmic examination including best-corrected visual acuity, IOP measurement, presence and degree of uveitis activity, presence of ocular complications including cystoid macular edema (CME), findings of slit lamp examination including presence and degree of cataract, findings of fundoscopic examination including cup to disc ratio.
  - Results of OCT and fluorescein angiography testing if clinically indicated ○ NEI-VFQ and EuroQoL administered.
  - Adverse event reporting
- Possibility of repeat dexamethasone pellet insertion ○ Adverse events related to the procedure will be collected (e.g., vitreous hemorrhage, elevated IOP, retinal detachment)
- **6-month examination** ○ Interval treatment history (current therapies for the treatment of uveitis, history of corticosteroid use including periocular corticosteroids, history of immunosuppressive drug use, need for IOP-lowering medications)
  - Interval ocular history (any complications due to uveitis, any ocular surgeries or procedures, history of glaucoma or ocular hypertension, treatment to lower intraocular pressure including laser procedures and/or surgeries
  - Ophthalmic examination including best-corrected visual acuity, IOP measurement, presence and degree of uveitis activity, presence of ocular complications including cystoid macular edema (CME), findings of slit lamp examination including presence and degree of cataract, findings of fundoscopic examination including cup to disc ratio.
  - Results of OCT and fluorescein angiography testing as clinically indicated ○ NEI-VFQ and EuroQoL administered.
  - Adverse event reporting
- Possibility of repeat dexamethasone pellet insertion or treatment with best medical judgment ○ Adverse events related to the procedure will be collected (e.g., vitreous hemorrhage, elevated IOP, retinal detachment)
- **9-month examination** ○ Interval treatment history (current therapies for the treatment of uveitis, history of corticosteroid use including periocular corticosteroids, history of immunosuppressive drug use, need for IOP-lowering medications)
  - Interval ocular history (any complications due to uveitis, any ocular surgeries or procedures, history of glaucoma or ocular hypertension, treatment to lower intraocular pressure including laser procedures and/or surgeries
  - Ophthalmic examination including best-corrected visual acuity, IOP measurement, presence and degree of uveitis activity, presence of ocular complications including cystoid macular edema (CME), findings of slit lamp examination including presence and degree of cataract, findings of fundoscopic examination including cup to disc ratio.

- Results of OCT and fluorescein angiography testing as clinically indicated ○ NEI-VFQ and EuroQoL administered.
- Adverse event reporting

- Possibility of repeat dexamethasone pellet insertion or treatment with best medical judgment ○ Adverse events related to the procedure will be collected (e.g., vitreous hemorrhage, elevated IOP, retinal detachment)
- **12-month examination** ○ Interval treatment history (current therapies for the treatment of uveitis, history of corticosteroid use including periocular corticosteroids, history of immunosuppressive drug use, need for IOP-lowering medications)
  - Interval ocular history (any complications due to uveitis, any ocular surgeries or procedures, history of glaucoma or ocular hypertension, treatment to lower intraocular pressure including laser procedures and/or surgeries
  - Ophthalmic examination including best-corrected visual acuity, IOP measurement, presence and degree of uveitis activity, presence of ocular complications including cystoid macular edema (CME), findings of slit lamp examination including presence and degree of cataract, findings of fundoscopic examination including cup to disc ratio.
  - Visual field assessment
  - Slit lamp photographs to assess cataract
  - Optic nerve photos
  - Results of OCT and fluorescein angiography testing as clinically indicated ○ NEI-VFQ and EuroQoL administered.
  - Adverse event reporting
- **Extended follow-ups** ○ Patients will continue to be followed at 3 month intervals after M12 according to standard of care until the common study close-out which will occur after the 2 year follow-up of the 20th enrolled patient
- Possibility of repeat dexamethasone pellet insertion or treatment at each of the 3 month extended follow-ups with best medical judgment ○ Adverse events related to the procedure will be collected (e.g., vitreous hemorrhage, elevated IOP, retinal detachment)

b. Study duration and number of study visits required of research participants.
   - Patients will be followed for a minimum period of 12 months.
   - A minimum of 9 visits (BL, Day 14, M1, M2, M3, M6, M9, and M12). If the PI/study ophthalmologist decides to insert another dexamethasone pellet, s/he may do so at M3, and/or M6, and/or M9, and/or at 3 month intervals thereafter (until the common study closeout) if indicated with best medical judgment

c. Blinding, including justification for blinding or not blinding the trial, if applicable.
   - N/A

d. Justification of why participants will not receive routine care or will have current therapy stopped.
   - N/A. Use of the dexamethasone pellet and immunosuppressive drug therapy are each part of standard clinical care in the treatment of active intermediate and posterior uveitis. The dexamethasone pellet is FDA-approved for the treatment of intermediate and posterior uveitis.

e. Justification for inclusion of a placebo or non-treatment group.
   - N/A. There is no placebo or non-treatment arm in this pilot study.

f. Definition of treatment failure or participant removal criteria.
   - N/A

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

- Since all treatments are currently used in the clinical care of uveitis patients, all patients enrolled in this study will be able to continue receiving therapy according to best medical judgment once the study ends.

5. Inclusion/Exclusion Criteria <u>Inclusion Criteria:</u>

- Active sight-threatening intermediate or posterior uveitis for which immunosuppressive drug therapy is planned and the physician is considering treatment with high-dose corticosteroid to control the uveitis whilst immunosuppressive drugs are being instituted or adjusted.
  - Note: it is acceptable for the patient to already be on an immunosuppressive drug as long as high dose corticosteroids are indicated.
- Patients must be age 18 years or older (the dexamethasone pellet is not FDA-approved for pediatric use) and sign an informed consent.
- The ocular media must be clear enough to obtain OCT and fundus photographs.
- No elective intraocular surgery should be planned for the first 3 months after enrollment.

<u>Exclusion Criteria</u>:

- Infectious uveitis
- History of scleritis
- Active or suspected viral infection of the cornea or conjunctiva
- History of mycobacterial or fungal disease
- HIV positivity
- Age <18 years old
- Allergy to dexamethasone
- Uncontrolled IOP
- Advanced glaucoma
- Aphakia with rupture of the posterior lens capsule
- ACIOL with rupture of the posterior lens capsule
- Media opacity that would preclude evaluation of the posterior pole via fundus photography or OCT assessment
- Planned elective ocular surgery within 3 months of enrollment - Any systemic disease requiring systemic corticosteroids.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

The fluocinolone acetonide implant is FDA-approved for the treatment of intermediate and posterior uveitis and it is equally effective in controlling uveitis as high-dose oral corticosteroids but avoids the systemic side effects associated with the use of high doses of oral corticosteroids. However, this form of local therapy has high rates of ocular side effects, including ocular hypertension causing glaucoma and/or requiring glaucoma surgery and cataracts. Furthermore, every two and half to three years the implant is exhausted of corticosteroid and therefore repeat surgical insertion of another implant may be required. A useful potential therapy for the treatment of these patients would be a shorter-acting local corticosteroid that could be delivered in conjunction with systemic immunosuppressive drug therapy that would have a lower ocular side effect profile but still would be effective enough to replace the use of high-dose systemic corticosteroids in the treatment of active intermediate and posterior uveitis. It is possible that the dexamethasone pellet could fill this unique role in the treatment of uveitis. We propose this proof of concept study to evaluate the dexamethasone pellet for this specific use among patients with active intermediate and posterior uveitis.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

- N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

- N/A. The dexamethasone pellet is FDA-approved for the treatment of intermediate and posterior uveitis.

7. Study Statistics

a. Primary outcome variable.

- Control of uveitis at the 1 month, 2 month, 3 month, 6 month and 12 month time points. Cumulative incidences of uveitis control will be compared to historical data from the Johns Hopkins cohort and from the Systemic Immunosuppressive Treatment of Eye Diseases (SITE) Research Group.

b. Secondary outcome variables.

- The cumulative incidence of control of inflammation (0.5+ or less vitreous cells in the liquid vitreous; trace or less anterior chamber cells; and inactive chorioretinal lesions) at the 3month visit and the 6-month visit will be compared to the published data (from Johns Hopkins and from the SITE database) of the cumulative incidence of steroid-sparing success (prednisone <=7.5 mg daily and controlled disease) and of oral steroid discontinuation with the goal of proving NON-INFERIORITY of the dexamethasone pellet. Cumulative incidences of ocular and systemic side effects of the dexamethasone pellet will be compared to those of oral prednisone via rates and cumulative incidences at 12 months.

c. Statistical plan including sample size justification and interim data analysis.

- 20 patients will be enrolled and the data regarding success of control of uveitis at the 6 and 12 month examinations will be compared with historical published data. Comparative data from the Johns Hopkins cohort, SITE database, and published MUST data will be utilized. d. Early stopping rules.

- None

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

- Dexamethasone pellet insertion within 14 days of the baseline visit and potential insertion at months 3, 6, 9, and every 3 months thereafter based on the study protocol and clinical judgment of the PI/study ophthalmologist.
- Dexamethasone pellet should not be used if patient is allergic to any of its ingredients.
- Injections into the vitreous in the eye may be associated with eye inflammation, subconjunctival hemorrhage, and transient increased eye pressure. Rarely, intravitreal injections may be associated with vitreous hemorrhage, retinal detachment, or endophthalmitis. The risk of performing an intravitreal injection as part of this study is no greater than that associated with clinical care in the treatment of uveitis. The study ophthalmologist will monitor the patient regularly after each injection.
- Use of corticosteroids (including dexamethasone) may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may increase the establishment of secondary eye infections due to bacteria, fungi, or viruses. However, these side effects have been reported to occur less frequently with the dexamethasone pellet than with other forms of intravitreal corticosteroids such as triamcinolone acetonide or fluocinolone acetonide. There may be a risk of the dexamethasone pellet moving into the anterior chamber of the eye in eyes in which cataract surgery has been performed. However, the risk is greatest in aphakic eyes or eyes with anterior chamber intraocular lens (ACIOL) in which the posterior capsule has been ruptured. Because of this, these eyes are excluded from this study.

- There are no major risks or discomforts associated with SD-OCT imaging, Humphrey Visual Field, visual acuity.
- Photographing of the eyes is low risk but may be uncomfortable because of the bright flashes of light used to take the pictures. The test takes about 5 to 10 minutes.
- Fluorescein angiography might cause nausea and vomiting in some patients.
- Overall, the mentioned risks above are not greater than those of standard clinical care with these patients.

b. Steps taken to minimize the risks.
- N/A. The risks associated with the treatment of uveitis in this study are no greater than those associated with routine care of a patient with these types of uveitis.

c. Plan for reporting unanticipated problems or study deviations.
- Adverse Event Reporting at each visit after the baseline visit. Which includes: Loss of three lines or greater of visual acuity, new onset cataract, new onset intraocular pressure (IOP) greater than 21 mm Hg, new onset intraocular pressure greater than 30 mm Hg, rise of IOP of 10 mm Hg or greater, need for cataract surgery, need for glaucoma surgery, complications of dexamethasone pellet insertion including, but not limited to: vitreous hemorrhage, retinal detachment and endophthalmitis.

d. Legal risks such as the risks that would be associated with breach of confidentiality.
- Risks to one's privacy will be addressed by collecting the data in a de-identified manner and stored in a locked office. The whole study will be conducted by JHU IRB certified research personnel based on HIPPA regulations.

e. Financial risks to the participants.
- The clinical visits will be charged to the patient's insurance as they are part of the clinical standard of care. The use of immunosuppressive drug therapy and its laboratory monitoring also will be charged to the patient's insurance.
- The dexamethasone implants are being provided by the study sponsor and therefore the patient will not incur a charge for this drug or procedure.

- All other study specific procedures such as (lens photos, visual field testing, optic disc photos will be covered by study sponsor.

9. Benefits

a. Description of the probable benefits for the participant and for society.
- The study participants may benefit from the treatment as all participants will be treated. We may learn of a new way to treat these type of patients that is as effective as oral prednisone but without the systemic side effects.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.
- Participants will receive $15.00 at each visit, to compensate their parking charge.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.
- Costs of procedures done only for the study are covered by the research funding from the study sponsor. The study participant and/or their insurance company will be responsible for the cost of the regular medical care, in the same manner as if the participant was not participating in this study.