INFORMED CONSENT FOR INTRAVITREAL AVASTIN™ (BEVACIZUMAB) INJECTION FOR RETINOPATHY OF PREMATURITY

INDICATIONS AND POTENTIAL BENEFITS

Retinopathy of Prematurity (ROP) is an eye disorder that affects premature infants. This disorder usually develops in both eyes and is one of the most common causes of visual loss in childhood. ROP can lead to lifelong vision impairment and blindness.

ROP was first diagnosed in 1942. It is a potentially blinding eye disorder that primarily affects premature infants weighing about 2¾ pounds (1250 grams) or less that are born before 31 weeks of gestation. The smaller a baby is at birth and the greater the prematurity, the more likely that the infant will develop ROP.

Several complex factors may be responsible for the development of ROP. The eye starts to develop at about 16 weeks of pregnancy, when the blood vessels of the retina begin to form at the optic nerve in the back of the eye. The blood vessels grow gradually toward the edges of the developing retina, supplying oxygen and nutrients. During the last 12 weeks of a pregnancy, the eye develops rapidly. When a baby is born full-term, the retinal blood vessel growth is mostly complete (The retina usually finishes growing a few weeks to a month after birth). But if a baby is born prematurely, before these blood vessels have reached the edges of the retina, normal blood vessel growth may stop. The edges of the retina—the periphery—may not get enough oxygen and nutrients.

Scientists believe that the periphery of the retina then sends out signals to other areas of the retina for nourishment. As a result, new abnormal vessels begin to grow. These new blood vessels are fragile and weak. The abnormal new vessel can leak and bleed, leading to retinal scarring. When these scars shrink, they pull on the retina, causing it to detach from the back of the eye or be distorted.

Research has shown that ROP is caused, at least in part, by the abnormal production of a substance called Vascular Endothelial Growth Factor (VEGF) in the eye. Avastin™ works by blocking the effects of VEGF.

The results have been so good with Avastin™ that some hospitals have completely discontinued the use of conventional laser therapy and now offer only the drug therapy to premature infants with this type of retinal disease.

ALTERNATIVES

The standard treatments for ROP are laser therapy or cryotherapy. Laser therapy "burns away" the periphery of the retina, which has no normal blood vessels. With cryotherapy, physicians use an instrument that generates freezing temperatures to briefly touch spots on the surface of the eye that overlie the periphery of the retina.

Both laser treatment and cryotherapy ablate (destroy) the peripheral areas of the retina, slowing or reversing the abnormal growth of blood vessels. The ablated retina no longer produces VEGF. Laser is generally felt to be superior to cryotherapy and has been the mainstay of treatment for many years.

Unfortunately, the treatments destroy some peripheral (side) vision. This is done to save the most important part of our sight—the sharp, central vision we need for "straight ahead" activities such as reading, sewing, and driving. Peripheral visual loss and progressive nearsightedness (myopia) commonly occur with ROP and with cryotherapy and laser treatments. Both laser and cryotherapy treatments are considered invasive surgeries on the eye. Both require heavy sedation and usually intubation.

Up to 25% (one out of every four) babies may still develop some significant visual loss, including blindness despite laser therapy. For some babies, the laser surgery may have to be repeated in order to adequately treat the ROP.

COMPARISON OF ALTERNATIVES

In a recent trial comparing laser therapy and Intravitreal Avastin™Injection , recurrence of ROP requiring additional treatment occurred in 4 infants in the Avastin™ group (6 of 140 eyes [**4%**]) and 19 infants in the laser-therapy group (32 of 146 eyes [**22%**]. Permanent retinal distortion was much more likely with laser treatment (22 of 146 eyes [**15.1%**]) than with Avastin™ treatment (1 of 140 eyes [**0.71%**]). The rate of retinal detachment was similar between the two groups. (2 of 140 [1.43%] with avastin vs 2 of 146 [1.37%] with laser. With Avastin™ treatment, the field of vision is usually completely preserved and the risk of myopia thought to be less with Avastin™ treatment than with cryotherapy or laser therapy.

PROCEDURE DESCRIPTION

Eye drops are administered to dilate the pupil before the procedure. Anesthetic eye drops are used to numb the eye. Antiseptic is applied to the eye to prevent infection.

An infant sized eye speculum is used to hold the eyelids apart during the procedure. A small syringe with a tiny needle is used to administer a small amount of the drug directly into the eye. The whole process takes two to three minutes. The medication is injected into the vitreous, or jelly-like substance in the back chamber of the eye.

After treatment with Avastin™ the abnormal vessels usually disappear and then normal vessels begin to grow again.

"OFF-LABEL" STATUS

Avastin™ was not initially developed to treat eye conditions. Based upon the results of clinical trials that demonstrated its safety and effectiveness, Avastin™ was approved by the Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer. As a condition of approval, the manufacturer produced a "label" explaining the indications, risks, and benefits. The label explains that Avastin™ works by blocking a substance known as vascular endothelial growth factor or VEGF. Blocking or inhibiting VEGF helps prevent further growth of the blood vessels that the cancer needs to continue growing.

Once a device or medication is approved by the FDA, physicians may, and commonly do, use the medication "off-label" for other purposes if they are well-informed about the product, base its use on firm science and sound medical evidence, and maintain records of its use and effects. Ophthalmologists are using Avastin™ "off-label" to treat several different eye conditions including ROP. Recently, a medication similar in function and designed for intravitreal administration was approved by the FDA for the treatment of Age Related Macular Degeneration and Retinal Vein Occlusions. That medication is not approved for the treatment of ROP and there are no studies on the use of that medication for ROP as there are for Avastin™.

POSSIBLE LIMITATIONS AND COMPLICATIONS

The goal of treatment is to prevent loss of vision. Although most patients treated for ROP with Avastin™ have had good results this treatment may not ultimately prevent loss of vision caused by the disease.

Treatment of ROP by Intravitreal Avastin™Injection is relatively new. It seems to provide many advantages over previous treatments. There may be yet be complications of this treatment that become recognized in the future that we do not yet now know about including developmental abnormalities and other systemic diseases.

Complications when Avastin™ is given to patients with cancer

When Avastin™ is given to patients with metastatic colorectal cancer, some patients experienced serious and sometimes life-threatening complications, such as gastrointestinal perforations or wound healing complications, hemorrhage, arterial thromboembolic events (such as stroke or heart attack), hypertension, proteinuria, and congestive heart failure.

Patients who experienced these complications not only had metastatic colon cancer, but were also given 400 times the dose your child will be given at frequent intervals, and in a way (through an intravenous infusion) that spread the drug throughout their bodies.

Risks for treatment for ROP include, but are not limited to:

- Failure to achieve the goal of surgery, (even with treatment, some infants develop severe visual loss, including blindness.)
- Damage to the retina (retinal detachment, retinal fold, or macular dragging or scarring)
- Bleeding in the eye (vitreous hemorrhage)
- Cataract formation (clouding of the lens of the eye)
- Glaucoma (increased pressure in the eye)
- Hypotony (reduced pressure in the eye)
- Eye infection (endophthalmitis).
- Damage to the iris (colored portion of the eye)
- Damage to the lens (cataract)
- Loss of vision or loss of the eye
- Loss of peripheral (side) vision
- Need for very thick glasses
- Corneal clouding or scarring
- Decrease or loss of circulation to the vital tissues in the eye
- Eye misalignment (strabismus)
- Eye enlargement
- Eye shrinkage
- Systemic complications, including the need to be on a ventilator, heart or respiratory collapse, and death.

Additional procedures may be needed to treat these complications.

CONSENT FOR INTRAVITREAL AVASTIN™ INJECTION FOR ROP

The ophthalmologist has explained to me the problem with my baby's eyes, and the risks,

benefits, and alternatives to Intravitreal Avastin™Injection for ROP. Although it is impossible for the doctor to inform me of every possible complication that may occur, the doctor has answered all my questions to my satisfaction. I understand that there is no guarantee that this procedure will prevent blindness in my child, and that other procedures may need to be performed and that this procedure may need to be repeated to effectively treat the baby for ROP.

In signing this informed consent for INTRAVITREAL AVASTIN™ INJECTION on behalf of my child, I am stating that I have been offered a copy, I understand the possible risks, benefits, and complications and:

- I have read this informed consent _____ **(parent's initials)**
- This consent form was read to me by

  _____ (**name).**

I wish to have Dr. Claron D. Alldredge, M.D. **perform** INTRAVITREAL AVASTIN™ INJECTION **on my child.**

_____ _____
Patient (or person authorized to sign for patient) Date/Time

_____ _____
Physician Signature Date/Time

_____ _____
Witness Signature Date/Time