Intravitreal Inserts

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Advances in biomedical engineering and ocular surgical techniques have encouraged the development of sustained release drug delivery implants to treat a variety of ophthalmic diseases. Polymer based drug delivery implants placed in the vitreous cavity have great efficacy in treating posterior segment diseases such as cytomegalovirus retinitis, uveitis, diabetic macular edema etc. Intermediate, posterior and panuveitis are typically the more severe forms of uveitis, resulting in highest incidence of visual loss. These forms of uveitis often require long-term systemic treatment with oral corticosteroids, often in conjunction with other immuno modulating therapy (IMT). Side effects of oral corticosteroids are many and can be life threatening; thus reduction of corticosteroid usage with the help of IMT is a primary goal in uveitis treatment strategy. While IMT and targeted biological agents are increasingly used as corticosteroid-sparing therapy, the fluocinolone acetonide implant is the first and currently the only sustained-release intraocular implant approved by the FDA for the long term control of non infectious posterior uveitis (Fig. 1). Its efficacy has been well documented. The multicentre uveitis steroid treatment (MUST) trial compares the efficacy of standardized systemic therapy vs. fluocinolone acetonide implant therapy for the treatment of severe cases of intermediate uveitis, posterior uveitis or panuveitis.

RETISERT (Fluocinolone Acetonide Intravitreal Implant)

Fluocinolone acetonide intravitreal implant is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. The drug substance is the synthetic corticosteroid, fluocinolone acetonide. It is less soluble in aqueous solution than dexamethasone (Fig. 2).

The fluocinolone acetonide implant is a sustained release system (Fig. 3) designed to deliver fluocinolone...
acetonide over 30 months. Each implant consists of a silicone elastomer containing fluocinolone acetonide 0.59 mg. It delivers drug at an initial rate of 0.6 micrograms/day over the first month, decreasing to a steady rate of 0.3 – 0.4 micrograms/day over approximately 30 months. \(^8,^9\) In patients with non-infectious posterior uveitis (NIPU), the implant reduces inflammation and preserves visual acuity over an extended period. Its most common side effects include elevated IOP and development of cataract. \(^10\)

Recently Callanan et al. \(^11\) published the 3-year clinical trial results from the Fluocinolone Acetonide Uveitis study group. The purpose of this multi-center, randomized study was to evaluate the safety and efficacy of 0.59 mg and 2.1 mg fluocinolone acetonide implants in NIPU. Uveitis recurrence in implanted eyes was reduced from 62% to 4%, 10.1% and 20% at 1, 2 and 3 years following implantation, respectively, for the 0.59 mg treatment group and from 58% to 7%, 17% and 41% respectively for the 2.1 mg treatment group. The rate of uveitis recurrence was low during the period corresponding to the active life of the implant but began to increase towards the end of the drug delivery period. There was no difference in the post-implantation uveitis recurrence rates between the 2 groups during the first 2 years following implantation, but there was a significant difference during the third post-implantation year, which was thought to be secondary to faster drug delivery with the original 2.1 mg implant. The need for adjunctive therapy to manage uveitis was significantly reduced after implantation, with 80% reduction in the use of systemic medication to control inflammation. Thus the fluocinolone acetonide implant is superior to intravitreal triamcinolone injection for uveitis. Implanted eyes had a higher incidence of IOP elevation (\(>10\) mm Hg) than non-implanted eyes and surgical mode of intervention was required in 40% of implanted eyes vs. 2% of non-implanted eyes to control the intraocular pressure.

Chich et al. \(^12\) reported recently that fluocinolone acetonide implant insertion can be combined safely with phacoemulsification and IOL implantation in the same surgical sitting in eyes with uveitis. Other applications for fluocinolone acetonide implants such as for macular oedema associated with central retinal vein occlusion \(^13\) and diabetes mellitus \(^14\) have been reported.

**Clinical Pharmacology:** Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen and scar formation associated with inflammation. Corticosteroids act by the induction of phospholipase A2 inhibiting proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common predecessor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

**Pharmacokinetics:** In a subset of patients who received the intravitreal implant and had blood samples taken at various times after implantation, plasma levels of fluocinolone acetonide were below the limit of detection (0.2 ng/ml) at all times. When aqueous and vitreous humor samples were assayed for fluocinolone acetonide in another subset of patients, detectable concentrations of fluocinolone acetonide was seen throughout the observation interval (upto 34 months), the concentrations were highly variable, ranging from below the limit of detection (0.2 ng/ml) to 589 ng/ml.

**Medidur:** The Medidur (Alimera) implant also contains fluocinolone, but it is much smaller. It is a reservoir implant, but it is not sutured to the eye wall and is allowed to float freely in the vitreous space.
**Posurdex**: Posurdex biodegradable dexamethasone implant (Allergan) is a different concept. It's biodegradable system is not reservoir based, it uses polymer and drug mixed together and the drug releases over time. As the polymer degrades, the drug is released.

**Dosage and Administration**: Each vitrasert implant contains a minimum of 4.5 mg of ganciclovir and is designed to release the drug over a 6 to 8 month period of time. The rate of release is approximately 1 $\mu$g/hr. Following depletion of ganciclovir from the implant, as evidenced by progression of retinitis, the implant may be removed and replaced.

**Contraindications and Complications of Intravitreal Implants**: 
As with any surgical procedure, potential complications accompanying intraocular surgery to place the implant into the vitreous cavity include cataract, increased intraocular pressure, vitreous loss, vitreous haemorrhage, retinal detachment, choroidal detachment, temporary reduction in visual acuity, endophthalmitis, hypotony and wound dehiscence. Following implantation of the implant, most patients experience an immediate and temporary reduction in visual acuity in the implanted eye which lasts for approximately two to four weeks postoperatively. All the patients should be monitored for elevated IOP regularly.

Retisert is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis, vaccinia and varicella and also in mycobacterial infections of the eye and other fungal infections.

Ganciclovir has the potential to cause temporary or permanent suppression of fertility in women and temporary or permanent inhibition of spermatogenesis in men. Vitrasert is contraindicated in pregnant and lactating women. Safety and effectiveness in pediatric patients below 12 years age have not been established.

**VITRAVENE (Fomivirsen Sodium Intravitreal Implant)**
Vitravene is indicated for the local treatment of cytomegalovirus (CMV) retinitis in patients with AIDS who are intolerant to or have a contraindication to other treatment for CMV retinitis.

**Conclusion**
Traditional treatment routes cannot obtain sufficient therapeutic concentrations for treatment of posterior...
segment diseases of the eye due to anatomic and physiologic protective mechanisms such as blood retinal barrier. For ideal drug treatment, the drug should reach the target tissue directly and at the desired time and concentration. For this purpose, liposomes, biodegradable polymers and non degradable implants have been developed in the last 20 years. Liposomes did not proceed beyond limited clinical studies due to a great deal of disadvantages. The most important disadvantage of non degradable implants are the need for surgery and wide incisions. Biodegradable polymers produce the best results due to properties like ease of implantation, no need to remove and excellent bioavailability. Thus intravitreal implants provide safe and effective therapy. Promising efficacy results show a significant reduction in recurrence rate and improvement in visual acuity.

References: