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New Drugs and New Posterior Delivery Methods in CME

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Abstract

Purpose—To discuss the characteristics, indications and adverse events (AEs) of sustained-release corticosteroid devices for the treatment of cystoid macular edema (CME).

Recent findings—Ozurdex® is approved for the treatment of diabetic macular edema (DME), retinal vein occlusion related-CME and noninfectious posterior uveitis (NIPU). It releases dexamethasone over a maximum period of 6 months making repeated intravitreal injections necessary for recurrent CME. Iluvien® releases fluocinolone for up to 36 months and is effective for the treatment of chronic DME. Retisert® (Bausch & Lomb, Rochester, NY) also releases fluocinolone, and is approved for chronic NIPU. Both Iluvien® and Retisert® are non-biodegradable devices and are highly associated with cataract and glaucoma.

Summary—Long-acting intraocular corticosteroid formulations offer a more predictable drug-release profile and reduced dosing frequency in comparison to conventional formulations of the same compounds but the risk-benefit ratio must be taken into consideration previous to the implantation of those devices.

Keywords

cystoid macular edema; dexamethasone intravitreal implant; fluocinolone acetonide; diabetic macular edema; retinal vein occlusion; noninfectious posterior uveitis

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Compliance with Ethical Guidelines

Conflict of Interest

Raquel Goldhardt, Renata Portella Nunes, and João Rafael de Oliveira Dias declare no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Background

Cystoid macular edema (CME) is a final common pathway for many ocular diseases. Corticosteroids have an important role in the therapeutic approach to vitreoretinal diseases, especially CME, where breakdown of the blood-retinal barrier causes increase in vascular permeability and molecular inflammatory mediators initiating a complex cycle.[1] In diabetics, corticosteroids target leukocyte adhesion suppressing the Intercellular Adhesion Molecule 1 (ICAM-1) gene expression. By inhibiting the leukocyte adhesion there is a decrease in the protein levels, less breakdown of the blood-retinal barrier ultimately decreasing vascular endothelial growth factor (VEGF) levels.[2–4] Recently, interleukin-8 (IL-8) was reported as one of the most significant inflammatory factors. It wasn't only correlated with central macular thickness, but with severity of the retinal ischemia.[5] The pathogenesis for ME in uveitis is still poorly understood, but in experimental models of uveitis, specific CD4+ T-cell-secreted cytokines play a central role in uveitic CME.[6] The various routes of corticosteroids include oral, intravenous, topical, periocular, and intravitreal.[7] Systemic side effects limit the administration of intravenous and oral steroids. While topical steroids often do not provide adequate posterior segment diffusion, intravitreal administration of steroids is extremely effective controlling intraocular inflammation, but carry serious risks such as ocular hypertension and cataract progression in eyes undergoing repeated injections.[8] Another significant potential complication is the increased risk of infectious or sterile endophthalmitis.[9]

There are currently three approved sustained-release corticosteroid implants: Ozurdex® (Allergan Inc., Irvine, CA), which releases dexamethasone (DEX); and Retisert® (Bausch & Lomb, Rochester, NY) and Iluvien® (Alimera Science, Alpharetta, GA), both releasing fluocinolone acetonide (FA). The physical characteristics, indications and duration effect are different for each device.

1. Dexamethasone Drug Delivery System

Ozurdex®—The DEX intravitreal implant (Ozurdex®, Allergan Inc., Irvine, CA) is a biodegradable polymer made of a poly (lactic-co-glycolic acid) (PLGA) matrix containing 700μg of DEX, which is released to the vitreous cavity over a period of 3–6 months.[10, 11] It is a water-soluble synthetic glucocorticoid, three times more potent than triamcinolone.[12] The drug–copolymer complex is inserted into the eye through the pars plana with a 22 gauge injector.[13] After the first two months, the DEX implant concentration declines, until the fourth month, and then maintains a lower concentration until month 6. The pharmacokinetic profile of the implant is similar in vitrectomized and nonvitrectomized eyes.[14]

The US Food and Drug Administration (FDA) approved the 0.7mg DEX implant (Ozurdex®) in 2009 for the treatment of CME secondary to retinal vein occlusion (RVO), and for the treatment of posterior noninfectious uveitis (NIPU). In 2014, the US FDA approved Ozurdex® for the treatment of diabetic macular edema (DME) in adults.[2]

A. Indications

1. Dexamethasone Implant for Retinal Vein Occlusion: RVO is a common cause of significant retinal ischemia and increased retinal vascular leakage in adults, with a great potential of visual loss.[15] CME secondary to branch (BRVO) or central retinal vein occlusion (CRVO) is an important cause of decreased visual acuity (VA) in those patients.[13]

Two randomized, prospective, masked, sham-controlled studies evaluated the safety and efficacy of DEX implant over an initial 6-month period followed by a 6-month open-label extension.[16, 17] Patients > 18 years of age with CME related to BRVO or CRVO were enrolled. Duration of CME had to be between 6 weeks and 12 months for BRVO and 6 weeks to 9 months for CRVO.[16] The proportion of eyes achieving an improvement of at least 15 letters of vision was greater in the treatment groups at month 1 and month 3. However, at month 6 this effect was not statistically significant anymore. The reduction in mean optical coherence tomography (OCT) central retinal thickness (CRT) was greater in the 0.7mg (208 ± 201μm) and 0.35mg (177 ± 197μm) groups than in the sham group (85 ± 173μm) at month 3 ($P < 0.001$), but not statistically significant at month 6.[8, 16] In the open-label extension, the adverse events (AEs) rate was similar between patients who received their first or second DEX implant, except for cataract. IOP increase in the groups treated with DEX implant was also noticed, which were usually transient and controlled with medications or observation. Also, 30% and 32% of the patients achieved an increase in 15 letters 60 days after the first and second DEX implant, respectively.[17]

2. Dexamethasone Implant for Noninfectious Posterior Uveitis: The efficacy of DEX implant in the treatment of NIPU was demonstrated in a multicenter study known as HURON (cHronic Uveitis evaluation of the intRavitreal dexamethasONe implant).[18] In this 26-week trial, eyes with noninfectious intermediate or posterior uveitis were randomized to receive a single treatment of 0.7mg DEX implant, 0.35mg DEX implant, or sham procedure. At all study visits, VA improvement of 15 or more letters from baseline was noticed more in those eyes that received the DEX implants in comparison to the sham group. Also, the proportion of eyes with a vitreous haze score of 0 at week 8 was higher in the eyes treated with 0.7mg DEX implant (47%), than in those treated with 0.35mg DEX implant (36%), and in the sham group (12%) ($P < 0.001$). Those results persisted through week 26. The percentage of eyes with intraocular pressure (IOP) of 25mmHg or more was at 7.1% in the 0.7mg DEX implant, 8.7% in the patients that received 0.35mg DEX implant, and 4.2% in the sham group. The incidence of cataract reported was 15% in the 0.7mg DEX implant group, 12% in the 0.35mg DEX implant group, and 7% in the sham group ($P > 0.05$).[18] Bilateral use of 0.7mg DEX implant in NIPU has also been reported in cases of Vogt–Koyanagi–Harada-related CME.[19]

3. Dexamethasone Implant for Diabetic Macular Edema: DME is the most frequent cause of visual impairment in diabetic retinopathy (DR), which is the result from plasma proteins leakage intothe macula.[2, 20] Corticosteroids act in multiple ways for the treatment of DME.[21] They are potent anti-inflammatory agents and inhibit VEGF expression.[3, 22]

A Phase 3 study evaluated the safety and efficacy of the 0.7 and 0.35mg DEX implants for the treatment of DME over a 3-year period.[23] In two combined trials 1,048 patients were randomized to receive the 0.7 or 0.35mg DEX implant or a sham injection. At the end of 3 years, 64.1% of the patients in the 0.7mg DEX implant group and 66.3% in the 0.35mg DEX implant group completed the study, in comparison to only 43.4% in the sham group. The DEX implant 0.7mg showed superiority in the gain of 15 letters or more from baseline to the final visit (22.2%) in comparison to the group that received 0.35 mg DEX implant (18.4%), or sham (12%; P<0.018). At the final follow-up, the mean standard deviation average reduction in CRT from baseline was −111.6μm in the 0.7mg and −107.6μm in the 0.35mg DEX implant, in comparison to −41.9μm in the sham group (P < 0.001). In addition, an increase in the CRT was only reported in the sham injection group after cataract surgery.[23]

The efficacy of 0.7mg DEX implant in refractory and persistent DME, initially treated with other modalities (laser, intravitreal anti-VEGF, or triamcinolone), has also been described.[24–26] A retrospective, interventional case series observed significant improvements from baseline VA and CRT at months 1, 3 and 6 after a single injection of 0.7mg DEX implant in patients with persistent DME.[25] A phase 2, prospective, multicenter, randomized, single-masked clinical trial BEVORDEX, intravitreal bevacizumab was compared to DEX implant for the treatment of DME.[26] Eyes were randomized to receive bevacizumab every 4 or 16 weeks, both *pro re nata*. Improvement in best corrected visual acuity (BCVA) of 10 or more letters was found in 40% of the eyes treated with bevacizumab and in 41% of the eyes treated with 0.7mg DEX implant (P=0.83). None of the eyes treated with bevacizumab lost 10 letters or more, whereas 11% of the eyes treated with DEX implant did, mostly because of cataract. A statistically significant decrease in CRT was observed in the eyes treated with DEX implant (−187 μm) in comparison to those treated with bevacizumab (−122 μm; P=0.015). Bevacizumab-treated eyes received a mean of 8.6 injections compared with 2.7 injections in the DEX implant group.[26]

4. Dexamethasone Implant in Vitrectomized and Nonvitrectomized Eyes: The pharmacokinetic profile of the 0.7mg DEX implant was reported to be similar in vitrectomized and nonvitrectomized eyes, which is important as other medications are less effective in vitrectomized eyes due to faster clearance.[14, 27] According to *Chang-Lin et al*, the concentration of DEX in the vitreous and retina was similar in vitrectomized and non-vitrectomized monkeys that received this implant.[14] In humans, the OZURDEX CHAMPLAIN study evaluated the efficacy and safety of 0.7mg DEX implant in vitrectomized patients with treatment-resistant DME.[27] In this prospective, multicenter, 26-week, phase 2 trial, 55 patients from Australia and US presenting treatment-resistant DME and a history of previous pars plana vitrectomy were enrolled. The maximum effect for the decrease of the CRT (−156μm; P<0.001) and for the increase in BCVA was obtained at week 8 (+6.0 letters; P<0.001). When this study finished 43% and 21% of the patients have gained 5 and 10 letters or more, respectively. A loss of at least 10 letters was observed in 11%, and of at least 15 letters in 7% of the patients at the last visit. At month 2, after the peak values, began a slight decrease in the BCVA and increase in the CRT, and those changes continued over 6 months.[27]

B. Safety and Tolerability of the Dexamethasone Implant: Due to the long exposure to the drug and relatively difficulty to remove the implant, the safety and tolerability of a sustained-release implant need to be assessed before its injections. In addition, the rate of drug release from the implant is crucial to maintain the concentration of drug inside the eye and at the vitreoretinal interface within the safe therapeutic window.[28]

According to *Boyer et al.*, who evaluated the safety and efficacy of DEX intravitreal implant in a three-years study in patients with DME, the incidence of AEs was 96.0% in the 0.7mg DEX implant group, 97.4% in the 0.35mg DEX implant group, and 80.3% in the sham group. These rates were influenced by the period of patient exposure to treatment, which was approximately 22% to 24% shorter in the sham group because of the high rate of discontinuations in the sham group during the first year of the study.[23]

Conjunctival hemorrhages due to injection procedure are one of the most frequent ocular AE, in addition to the rise in the IOP and cataract.[2, 11, 26, 27, 29, 30] Retinal tears, endophthalmitis, retinal detachment, and hypotony are rare ocular events described in less than 2% of the patients submitted to the DEX implant.[23] Vitreous hemorrhages, eye pain and floaters have also been described.[4, 23, 26] Migration of the DEX implant into the anterior chamber has been described in aphakic and pseudophakic patients, especially with iris-claw intraocular lens, but also in a pseudophakic patient with intact posterior capsule.[31–40] The anterior migration of the DEX implant can cause complications such as secondary corneal decompensation. In these cases, surgical removal of the implant is mandatory.[40]

A trial evaluated the efficacy of 0.7 mg and 0.35mg DEX implant to an observation group for the treatment of CME of various etiologies. In this study, ocular AEs occurred in all the treatment groups, including anterior chamber inflammation, vitreous hemorrhage, and ocular pain or irritation, especially within the first 7 days after injection. Both anterior chamber flare (5%) and elevated IOP (6%) were higher in the 0.7mg group only.[11]

One of the other major AEs of concern for corticosteroids is the development or progression of cataracts in phakic patients. The 3-year data from the MEAD study, a 3-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema showed that the incidence of cataracts from baseline in the phakic patients was statistically higher in patients submitted to the 0.7mg DEX implant (67.9%) in comparison to the 0.35mg DEX implant (64.1%) and sham injection groups (20.4%).[23] When the DEX implant plus laser versus laser alone were compared, the cataract progression in the phakic eyes was statistically higher in the DEX implant group (22.2%) in comparison to the laser alone group (9.5%) ($P = 0.017$) at 12 months. However, surgery rates did not differ between the groups.[2, 29] In the BEVORDEX study, increases in the cataract grades were 13% in the 0.7mg DEX implant group and 4.8% in the bevacizumab group. Likewise, 6.5%, and 2.4% of the patients required surgery for cataracts in the 0.7mg DEX implant and bevacizumab groups, respectively.[26]

Increase in IOP also is considered a common AE that may occur after the DEX implant. In the MEAD study, one-third of patients in each DEX implant treatment group had a clinically

significant increase in IOP that required treatment. None of the patients underwent removal of the implant to control IOP, and only 1 patient (0.3%) in each DEX implant treatment group underwent glaucoma incisional surgery because of the IOP elevation. Mean IOP returned to baseline levels by 6 months after the DEX implant injection. Besides, an additional increase of IOP was not observed in year 2 or 3, and the proportion of patients using IOP-lowering medications in the study eye remained similar from year to year, suggesting that there was no cumulative effect of DEX implant on IOP. Furthermore, there were no arterial thromboembolic AEs considered by the investigator to be related to treatment and no evidence of local or systemic delayed wound healing.[23]

This implant is contraindicated in patients with advanced glaucoma, periocular infections and in those with not intact posterior lens capsule because of the risk of implant migration to the anterior chamber.[34]

2. Fluocinolone Acetonide Intravitreal Implant

A. Retisert®—In 2005, US FDA approved the fluocinolone acetonide (FA) intravitreal implant 0.59mg (Retisert®, Bausch & Lomb, Rochester, NY, USA) for the treatment of chronic noninfectious posterior uveitis. The FA implant is a non-biodegradable implant and, based on a Phase 3 study, has demonstrated favorable results in the control of uveitis.[41] The implant consists of a pellet with 0.59mg fluocinolone coated with polyvinyl alcohol (PVA) and silicone laminates and provides sustained drug delivery over a period of 2.5 to 3 years. The implant is a very small device that consists of a tablet encased in a silicone elastomer cup containing a release orifice and a PVA membrane positioned between the tablet and the orifice. The silicone elastomer cup assembly is attached to a PVA suture tab with silicone adhesive.[42–44] Fluocinolone is a corticosteroid with a high potency, low solubility and a very short duration of action in the systemic circulation.[45]

Retisert® was developed to provide sustained release of fluocinolone directly to the vitreous cavity over a prolonged period of time, avoiding complications with systemic therapy or repeated corticosteroid injections. It is inserted into the posterior segment through pars plana incision and sutured to the sclera. It releases FA at an initial rate of 0.5–0.6μg/day, decreasing over the first month to a steady state between 0.3 and 0.4μg/day for approximately 2.5 years.[46]

During the course of its development, this drug was evaluated in three large multicenter clinical trials. Thirty-four-week and 3-year results of the first trial and 2-year results of the second trial have already been published.[41, 47] The objective of the 3-year, multicenter, clinical trial conducted by *Callanan et al* was to evaluate the safety and efficacy of the 0.59mg and 2.1mg FA intravitreal implants in subjects with uni or bilateral NIPU for a 3-year study period. The results from this study demonstrated that the FA intravitreal implant was highly effective in controlling inflammation secondary to NIPU.[47] The uveitis recurrence rates in implanted eyes until the third year post-implantation were significantly lower than the 1-year pre-implantation rate in the same eyes regardless of the dose. However, the uveitis recurrence increased by the end of the drug delivery period. In the 0.59mg FA implant group, uveitis recurrence rates were extremely low during the first and second year post-implantation periods but increased to 20% during the third post-

implantation period. In contrast, in the eyes that received 2.1mg FA intravitreous implant, the recurrence rates were significantly lower during the 1- and 2-year post-implantation periods but increased to 41% during the third year.[47]

The proportion of eyes with a reduction in the CME area was greater in implanted eyes versus non-implanted fellow eyes at the 1- and 3-year post-implantation visits. At the 1- and 3-year post-implantation visits, there was a reduction in the area of CME in 86% and 73% of implanted eyes, respectively, compared to 28% and 28% of the fellow non-implanted eyes, respectively, in the 0.59mg implant group. In the 2.1mg FA implant group the reduction in the area of CME was observed in 70% and 45% of implanted eyes, at the 1- and 3-year visits, respectively, compared with 27% and 22% of fellow non-implanted eyes, respectively, ($P < 0.01$).[41, 47]

In patients with baseline CME, a significant correlation ($r = 0.2$, $P < 0.05$) between change in VA and change in CME was reported.[41, 47]

Safety and Tolerability of Retisert®: Regarding the ocular AEs over 3 years after implantation, a study showed that cataract surgery was required in 93% of the cases, and elevated IOP was observed in 67%, with 5.8% undergoing glaucoma filtering procedures.[41] Other side effects noticed in the initial trials included visual field loss, pain, conjunctival hyperemia, conjunctival hemorrhage, blurred vision, hypotony, retinal detachment, and endophthalmitis. Other rare but potentially severe ocular AEs include nonfunctioning implants, formation of vitreous bands, cytomegalovirus retinitis and endothelitis, scleral melt and herpes simplex necrotizing retinitis.[47–54] Procedure-related complications described include implant expulsion, implant migration, and wound dehiscence.[55]

Many patients with recurrent NIPU need to implant a new device.[48, 56] The second implant can be inserted at a new incision site or the old implant can be removed and a new one placed at the same site. The idea of inserting the implant at the same site is that during a patient's life many implants should be necessary and the wounds near these devices heal slowly because of the presence of a steroid. There have been reports of dissociation during implant exchange procedures with subsequent cases of retinal tear or suprachoroidal hemorrhage.[57–59]

Further evidence to support the use of Retisert® in vision threatening NIPU stems from the Multicenter Uveitis Steroid Treatment (MUST) trial, a randomized controlled clinical trial that compared local therapy with FA intraocular implant with systemic corticosteroid therapy supplemented, when indicated, by corticosteroid-sparing therapies.[60] Study results indicated that, in each treatment group, mean BCVA improved over 24 months, with neither approach being superior to the other.[61] Therefore, the specific advantages and disadvantages associated with each treatment should guide the treatment selection, also considering individual patients' particular circumstances.[61, 62] This drug is also used off-label in other retinal diseases that include DME and CRVO.[63, 64]

Retisert® is contraindicated in active mycobacterial, bacterial, fungal, and viral eye infections.[55]

B. Iluvien®—Control Delivery Systems (now pSivida, Inc.,Watertown, MA), following the development of Retisert®, created an injectable implant to allow administration into the vitreous through a 25-gauge needle. Iluvien® (Alimera Sciences Limited, Aldershot, UK) was designed to deliver corticosteroid to the retina for up to 3 years. It is a non-biodegradable microimplant containing FA, composed of polyimide and measuring 3.5×0.37mm. It is injected into the eye in day care setting with a 25-gauge needle in the pars plana.[55] Once injected the microimplant continuously releases a low dose of FA into the vitreous (0.2μg/day FA) that lasts for up to 36 months.[65] Although it uses same drug matrix as Retisert®, it releases the drug at a lower dose (0.2 or 0.5μg/day versus 0.59μg/day with Retisert®).[61]

Iluvien® was approved by US FDA on September 26, 2014 for the treatment of chronic DME.[65, 66] The FAME (“Fluocinolone Acetonide in patients with diabetic macular edema”) study reported the combined 3-year results of two trials with Iluvien® in patients with chronic DME. In this study, patients with persistent DME were evaluated after one or more laser treatments, and randomized 1:2:2 for sham injection, low-dose FA implant (0.2μg/d), or high-dose FA implant (0.5μg/d). At 36 months, 27.8% (high dose) and 28.7% (low dose) of all treated eyes versus 18.9% of sham eyes had an improvement of at least 15 letters (P=0.018). Continued follow-up showed the maintenance of those results for at least 3 years.[67]

In a subgroup analysis, it was suggested that patients with persistent DME who tend to respond poorly to many treatments, including focal/grid laser photocoagulation, respond well to administration of a FA insert.[67]

Safety and Tolerability of Iluvien®: Cataract was the most commonly seen ocular AE found in the FAME study, which was noticed in 42.7% phakic eyes of the low-dose group, 51.7% of the high-dose group, and 9.7% of the sham group. The median time for cataract detection was 12 months and the median time for cataract surgery was 18 months. Eighty percent of the phakic eyes in the low dose group were submitted to cataract surgery by the end of the study, and 87.2% of those in the high dose group, in comparison to 27.3% in the sham group. Overall, IOP-related AEs were more frequent in the FA insert groups (low dose, 37.1%; high dose, 45.5%; sham, 11.9%). Incisional IOP-lowering surgery was necessary in 8.1% in the high-dose group, 4.8% in the low-dose group, and 0.5% in the sham group.[67]

Migration of the implant to the anterior chamber was described in one vitrectomized patient with previous posterior capsule rupture. The implant was promptly removed in order to prevent corneal decompensation.[68]

Iluvien® is also under investigation in Phase 2 studies for the treatment of wet and dry age-related macular degeneration, RVO, and chronic noninfectious uveitis. This implant is contraindicated in the presence of glaucoma and active mycobacterial, fungal or viral infection.[55]

3. Other Posterior Segment Drug Delivery Devices Under Investigation

The Cortiject® implant (NOVA63035, Novagali Pharma S.A.) is a preservative-free injectable emulsion containing a tissue-activated corticosteroid prodrug. The prodrug is converted into DEX by enzymes present in the retina and choroid and a single intravitreal injection provides sustained release for up to 9 months. A Phase 1 study with Cortiject® for DME is currently ongoing.[55]

I-vation® (SurModics, Inc.) is an implant that contains 0.925μg triamcinolone acetonide (TA). It releases the drug for up to 2 years and is injected in the eye with a 25-gauge needle. This implant consists in a titanium helical coil coated with PVA-EVA polymers and a thin cap, and measures 0.4mm long by 0.21mm wide. The cap stays under the conjunctiva and provides rapid retrieval of the implant later on if needed. A Phase 1 trial showed reduction in DME 24 months after the implant insertion. However, this trial was suspended when study data released in 2008 favored focal/grid photocoagulation over preservative-free intravitreal TA for DME.[69]

The iTrack microcatheter (iScience Interventional) is a device used for suprachoroidal drug delivery. It includes an optical fiber that allows transmission of light to the tip to guide surgical insertion.[55] The safety, feasibility, and preliminary efficacy of an iTrack microcatheter containing bevacizumab and TA was studied in a pilot study with 6 eyes with severe subfoveal hard exudates.[70] Severe subfoveal hard exudates were almost completely resolved in all the eyes, and BCVA improved by ≥2 lines in 4 eyes and remained stable in 2 eyes. There were no surgical or postoperative complications.[70]

The PLGA microspheres with TA (RETAAC system) were also studied in human subjects. [71, 72] In a Phase 1/2 study, patients with DME refractory to laser showed a reduction in CRT 3 months after the RETAAC injection, and remained stable for up to 12 months. No side effects were observed in this study[55, 72].

With the biodegradable Verisome®™ drug delivery technology (Icon Bioscence Inc.), drugs cans be injected into the vitreous by a 30-gauge needle as a liquid. When the drug is injected, it coalesces into a single spherule that settles inferiorly.[55] In a prospective Phase 1 clinical trial, 10 patients with chronic ME due to RVO were submitted to a single intravitreal injection of TA (IBI-20089). Two cohorts of five patients received an intravitreal injection of the sustained liquid drug delivery system containing 6.9 mg or 13.8 mg of TA. A statistically significant decrease on the CRT at day 360 was seen only on cohort 2. AEs included elevated IOP in two patients with neovascular glaucoma due to CRVO, and corticosteroid-induced increased IOP in one patient, who required a glaucoma tube shunt. [73]

Medidur (pSivida Corp.) is an injectable micro-insert that comprises the same insert as Iluvien®, but provides sustained release of 0.18 mg of FA, at a controlled rate directly to the retina for three years. Two Phase 3, randomized, sham injection-controlled trial were conducted to assess the safety and efficacy of Medidur for the treatment of NIPU. The first Phase 3 Medidur trial achieved the primary efficacy endpoint of preventing the recurrence of

posterior uveitis at six months. A similar trial is still being conducted and patients are being enrolled.[73]

Table 1 summarizes the drug delivery systems for the treatment of CME (Table 1).

Conclusions

New technologies are transforming patient lives with significant improvement in quality of life.[74] The sustained-release intravitreal drug sustained-release technology for CME has revolutionized therapy and improved patient quality of life. In order to avoid the obstacles associated with topical and systemic administration of medicines, these high-tech pellets and implants were developed making possible to achieve the desired intravitreal therapeutic level with fewer side effects. However, the risk-benefit ratio, as well as the cost of these medications, will be critical to their implementation and acceptance in the clinical settings.

Ozurdex® appears to have less AEs with a favorable IOP profileand has been proved to be an alternative treatment for DME, NIPU, and RVO related-CME. However, in chronic cases various injections may be performed because the drug release takes no longer than 6 months. Iluvien® is a smaller tube that releases fluocinolone, indicated for the treatment of chronic DME, and may be less invasive than both the dexamethasone device and Retisert®, but is non-biodegradable. The fluocinolone implants last longer but their use is associated with a higher risk of cataract and IOP increase, many times demanding surgery. Retisert® lasts up to two and half years, and may be an option for the treatment of chronic NIPU, however requires surgery for scleral fixation.

Other techniques to deliver drugs into the eye are being tested, including using iontophoresis, external or internal reservoirs, and various implants. Although an optimal device is yet to be created for the treatment of CME related to various conditions, the development of the current sustained-release corticosteroids technology represents a great advance in vitreoretinal pharmacotherapy.

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Table 1

Posterior Segment Drug Delivery Systems for the Treatment of Cystoid Macular Edema (CME)

Drug released	Commercial name	Indication	Administration	Current status	Drug-release duration
Dexamethasone 0.7mg	Ozurdex	RVO, NIPU, DME	Intravitreal injection (22-gauge aplicator)	FDA approved	6 months
Fluocinolone Acetonide 0.59mg	Retisert	NIPU	Small pars plana incision; Sutured to the sclera.	FDA approved	2.5 years
Fluocinolone Acetonide 0.19mg	Iluvien	Chronic DME	Intravitreal injection (25-gauge aplicator)	FDA approved	3.0 years
Dexamethasone	Cortiject	DME	Intravitreal injection	Phase I study	6–9 months
Triamcinolone acetonide 0.925μg	I-vation	DME	Intravitreal injection (25-gauge aplicator)	Phase 2 suspended	2 years
Triamcinolone acetonide (IBI-20089)	Verisome	DME	Intravitreal injection (30-gauge aplicator)	Phase I	1 year

Legends:
RVO – Retinal vein occlusion
NIPU – Noninfectious posterior uveitis
DME – Diabetic macular edema
FDA – Food and Drug Administration