Principles and Practice of Intravitreal Application of Drugs

IV.E.

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References

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Key Concepts

1. Intravitreal drug delivery provides a higher potency of drug to the retina and choroid, but is often short-lived, thus underscoring the need for sustained delivery methods.
2. There are advantages and disadvantages to biodegradable and nonbiodegradable sustained drug delivery devices.
3. New pharmacologic targets and methods of sustained drug delivery may transform the method of treatment of many retinal and choroidal diseases. Vitreous structural variations can influence pharmacokinetics and must be taken into consideration for new drug delivery systems to be effective at different ages and in different disease states.

I. Introduction

Over the last 10 years, the success of anti-vascular endothelial growth factor (VEGF) antibodies for the treatment of neovascular age-related macular degeneration (AMD) has made the use of intravitreal injections for the treatment of posterior segment disease commonplace. The application of drugs into vitreous, as either a direct intraocular injection or in the form of sustained-release devices, is currently the focus of many clinical studies to treat a number of retinal and choroidal diseases. The advantages of this approach are that local treatment bypasses the systemic side effects of a drug

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and enables more direct control over the dose and duration of drug delivery to the target site. Furthermore, as we gain an increased understanding of the pathophysiological processes in diseases such as vitreomacular traction syndrome and diabetic retinopathy, new pharmacologic treatments have arisen that have the potential to obviate the need for surgical intervention or at least facilitate surgery [see chapter VI.A. Pharmacologic vitreolysis]. As technology and our understanding of disease processes evolve, these treatments will undoubtedly become more refined both in the way they are delivered and in the specificity of the pharmacologic target. This chapter reviews the principles of intravitreal drug delivery for both short-term and sustained-release formulations.

II. Fundamental Principles of Intravitreal Drug Delivery

The challenge of treating posterior segment disease resides in the obstacles encountered while trying to achieve therapeutic drug concentrations at the level of the retina and choroid. Topically administered drug that is not lost immediately to the systemic circulation (90–95 % is lost through nasal and conjunctival vessels into the systemic circulation) is absorbed through the cornea into the anterior chamber where it is eliminated through the trabecular meshwork. Drugs delivered to the sub-Tenon's space can penetrate the more permeable sclera to achieve higher concentrations in the retina and choroid. However, both the tight junctions of the retinal pigment epithelium (RPE) and dissipation of drug due to choroidal blood flow limit access of drugs to the retina, although lipophilic molecules may penetrate. Systemically administered (either intravenous or oral) drugs are one avenue to circumvent some of these barriers, especially if the drug is lipophilic and is therefore able to bypass the blood-retinal barrier. The systemic side effects from high enough concentrations of drug required to attain intraocular efficacy, however, limit the utility of many systemically administered drugs [1, 2]. Alternatively, drugs administered intravitreally can attain high enough concentrations for direct treatment of retinal conditions. Drugs delivered intravitreally are eliminated by outflow through either the anterior route, composed of the trabecular meshwork, or the posterior route, through the blood-retinal barrier, into the systemic circulation [1, 3].

The ideal drug formulation for intravitreal administration would require a number of qualifications. First, the drug should have a long enough half-life that does not mandate repeated injections and risk of complications. Anti-VEGF agents require repeated injections because they have short half-lives and first-order kinetics (Figure IV.E-1a, c) [4, 5]. Intravitreal steroids, such as triamcinolone, are biphasic, or follow a two-compartment model with exponential decline initially, followed by first-order kinetics after 1 month (Figure IV.E-1a, b) [6]. Some of the newer sustained-release steroid devices can demonstrate zero-order kinetics (flat line shown in Figure IV.E-1a), thus releasing a constant amount of therapeutic level steroid for the lifespan of the implant (Figure IV.E-1d) [7]. Second, the ideal intravitreal drug formulation should not interfere with the transparency of the ocular media as not to interfere with vision. This is an important consideration for microsphere and nanosphere technology where a larger particle size or more numerous particles can cause visual obscuration. A third requisite for an intravitreally administered drug is that it should be delivered at a therapeutic dose that does not cause toxicity or impede normal cellular activity [3]. By providing a constant lower concentration of drug over time (zero order) rather than larger spurts of drug that decrease rapidly (first order), sustained-release devices are advantageous in that they provide therapeutic levels of drug without as much local and systemic toxicity.

Sustained-release devices now available or under investigation are shown in Figure IV.E-2. They include devices that are suspended in the vitreous cavity by fixation to the sclera, injected into the suprachoroidal space or into the vitreous cavity as a free-floating device, or placed underneath the conjunctiva or into the sclera.

III. The Practice of Intravitreal Injection of Drugs

A. Technique for Intravitreal Drug Injection

Topical proparacaine followed by 4 % lidocaine soaked into a cotton-tip applicator or subconjunctival 2 % lidocaine is commonly used over the injection site. The site is commonly located inferotemporally to avoid drug deposition into the visual axis by gravity or, alternatively, in the superotemporal quadrant to avoid contamination with the accumulation of bacteria in the tear lake of the inferior fornix. An eyelid speculum is placed in the eye to keep the eyelashes away from the injection site. A 5 % povidone-iodine solution is then applied to the eye and then irrigated. The pars plana is marked with an empty tuberculin syringe or calipers 3.5–4 mm behind the limbus. A half-inch 30 or 32 G needle on a tuberculin syringe containing 0.05–0.1 mL of the medication is then introduced into the mid-vitreous cavity. When the needle is removed, the site is tamponaded with a sterile cotton-tip applicator to prevent reflux of drug. Postinjection topical antibiotics are not required.

B. Special Considerations in Infants

Pars plana location varies with infant development and can be located 1–1.5 mm behind the limbus in premature infants,

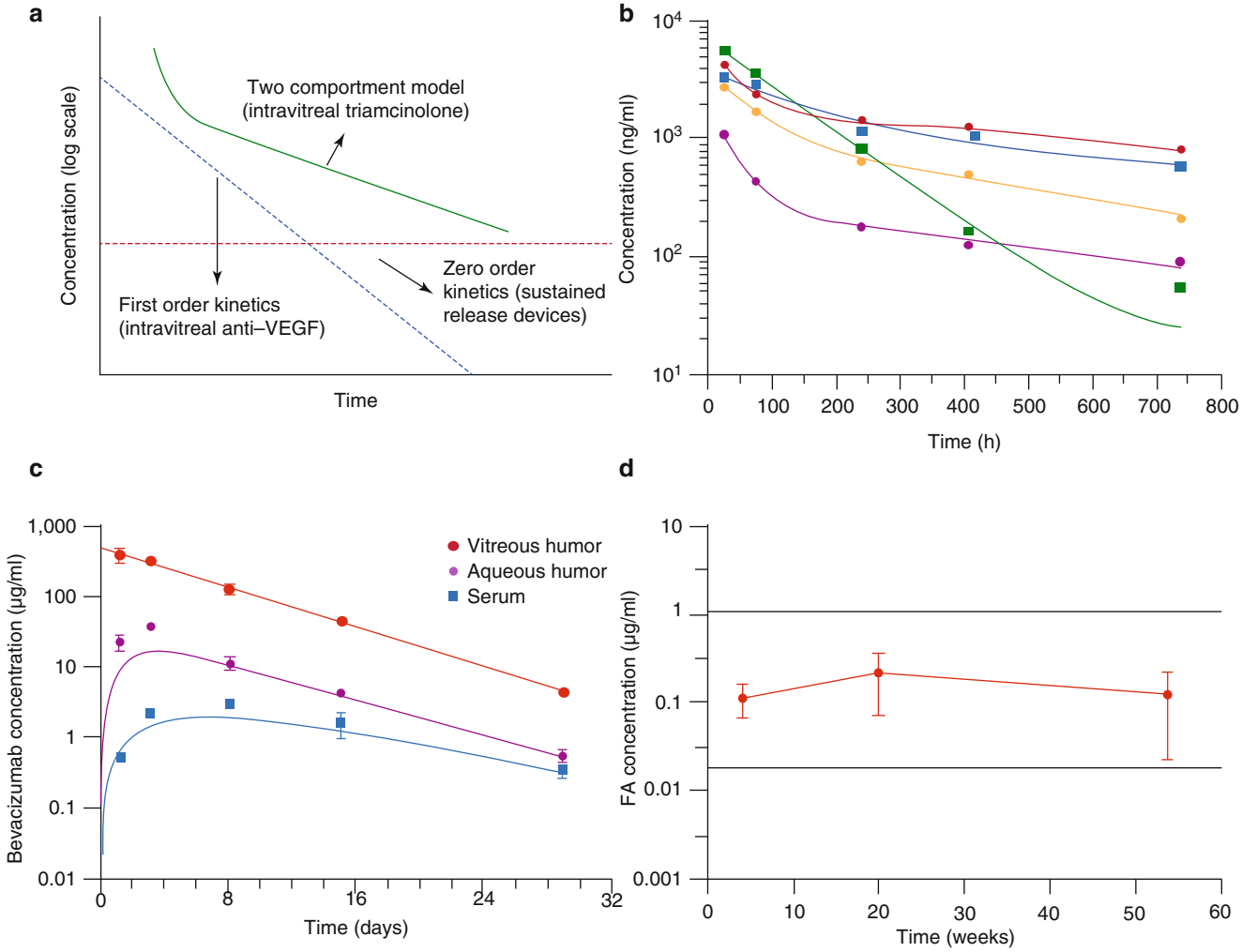

Figure IV.E-1 (**a**) First-order (*blue dotted line*), zero-order (*red dashed line*), and two-compartment model (*green line*) elimination kinetics shown in log scale. (**b**) Two-compartment model pharmacokinetics of triamcinolone in the vitreous cavity with different lines from different patients. (**c**) First-order kinetics exhibited by bevacizumab given intravitreally. (**d**) Fluocinolone acetonide sustained delivery device (Retisert [4, 5]) exhibits zero-order kinetics (Jaffe et al. [7])

but is 2–3.5 mm from the limbus in full-term infants. This affects the approach to needle placement during intravitreal injections [8]. Accordingly, the vitreous volume in infants is approximately two-thirds to three-fourths that of adults, thus requiring adjustments in administered drug volume so as not to increase intraocular pressure too severely or cause drug toxicity to the retina.

C. Complications

Complications associated with intravitreal injections include pain, vitreous hemorrhage, subconjunctival hemorrhage, transient elevation of intraocular pressure, infectious endophthalmitis, uveitis, or sterile endophthalmitis. The rate of infectious endophthalmitis following intravitreal injections has been reported to be between 0.1 and 0.16 % per injection and appears to be minimized using a standardized sterilization protocol including the use of povidone-iodine and eyelid specula [9] (see above). Sterile endophthalmitis was reported in 1–2 % of patients receiving intravitreal injection of non-preservative-free triamcinolone and can occur in patients receiving Avastin as well [10]. In a Medicare claims database case-control study, the rates per injection after anti-VEGF treatment of endophthalmitis (0.09 %), vitreous hemorrhage (0.23 %), and uveitis (0.11 %) were higher than in the control group [11]. Rates of rhegmatogenous retinal detachment and retinal tear do not appear to be significantly higher in patients who received intravitreal anti-VEGF agents than age-matched controls [11]. Furthermore, several reports have now shown that sustained elevation of intraocular pressure can occur in susceptible individuals who receive repeated injections of anti-VEGF agents [12–15]. In a head-to-head trial of ranibizumab with bevacizumab, two-year

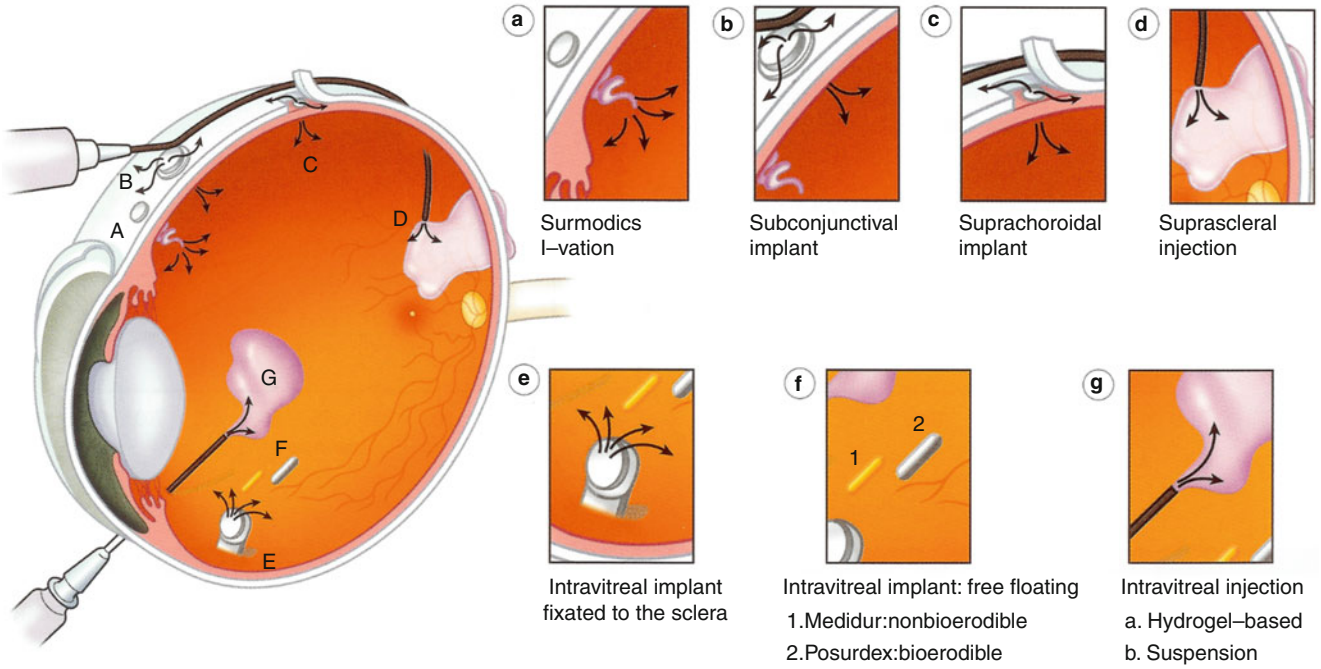

Figure IV.E-2 Drug delivery systems and their anatomical location (Adapted from Lee and Robinson [93]; Spaeth GL et al. [95])

data showed that overall systemic adverse events were low, but there appeared to be a slightly higher prevalence of overall systemic adverse events in patients treated with bevacizumab although there was no difference in arteriothrombotic events, and the events that were captured as differences have not been previously associated with anti-VEGF therapy [16]. Since then, a meta-analysis safety review of this issue has been unable to determine the relative safety of these drugs because most head-to-head studies were not designed to adequately monitor for systemic adverse events [17].

IV. Intravitreal Drug Therapy

A. Short-Term Therapy

1. Antibacterial Agents

The mainstay of empiric treatment for bacterial endophthalmitis employs the use of ceftazidime, a third-generation cephalosporin with increased activity against gram-negative organisms, and vancomycin, the drug of choice for methicillin-resistant *Staphylococcus aureus* and other gram-positive organisms [18]. Levofloxacin is a third-generation fluoroquinolone with activity against gram-positive and gram-negative bacteria. Rabbit models have shown similar antibacterial activity of 1.5 % levofloxacin against *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* in comparison to standard intravitreal vancomycin and ceftazidime [19]. Recent evidence supports the safety of intracameral moxifloxacin after anterior segment surgery [19], which can very likely be used safely in vitreous as well (Table IV.E-1).

2. Antifungal Agents

Fungal endophthalmitis is most commonly treated with intravitreal amphotericin B, which has been shown to be effective against most *Candida* species as well as *Aspergillus*, *Rhizopus*, and *Penicillium*. Doses up to 10 μg have been shown to be nontoxic, although there have been reports of retinal necrosis when injected too close to the retina [20]. The liposomal formulation of amphotericin B has been shown in animal models to have less toxicity to the retina. Koc and colleagues have reported a case of liposomal amphotericin B used after vitrectomy in the treatment of *Candida* endophthalmitis without any known ocular toxicity [21]. Among the newer generation triazoles (voriconazole, ravuconazole, posaconazole) that have broad antifungal coverage with relatively low toxicity, only voriconazole has been given intravitreally in humans. The short half-life of voriconazole results in the requirement for close observation with frequent repeated injections (Table IV.E-1). Sen et al. demonstrated in their case series that five patients who had fungal endophthalmitis resistant to fluconazole and amphotericin B responded to intravitreal voriconazole [22]. Although the echinocandin caspofungin does not appear to reach therapeutic levels in vitreous when given systemically, this agent shows promise as an intravitreal agent against *Candida* and *Aspergillus*. Kusbeci and colleagues demonstrated its

Table IV.E-1 Dosage and half-life of antibiotics given as intravitreal injections

Agent	Intravitreal dose	Half-life in vitreous (hours)	Coverage
Antibacterial			
Vancomycin	1 mg	30	Gram +, MRSA
Ceftazidime	2.25 mg	16	Gram +, gram –, anaerobes
Amikacin	0.4 mg	24	Gram +, gram –
Gentamicin	0.2 mg	12–35	Gram +, gram –
Gatifloxacin	0.4 mg[a]		Gram +, gram –, *Pseudomonas*, anaerobes
Moxifloxacin	0.05–0.16 mg[a]	1.72	Same as above
Antifungal			
Amphotericin B	5–10 µg	6.9–15.1	*Candida*, *Aspergillus*, *Penicillium*, *Rhizopus*
Fluconazole	100 µg	3.1	*Candida*, *Aspergillus*, *Histoplasma*, *Fusarium*
Itraconazole	10 µg		Same as above
Voriconazole	50–100 µg	2.5	Same as above
Antiviral			
Acyclovir	240 µg		HSV, VZV
Ganciclovir	2–5 mg	7–8	HSV, VZV, CMV
Foscarnet	1–2.4 mg	77	HSV, VZV, CMV
Cidofovir	20–100 µg	24.4	HSV, VZV, CMV

[a]Extrapolated from animal studies
MRSA methicillin-resistant *Staphylococcus aureus, HSV* herpes simplex virus, *VZV* varicella zoster virus, *CMV* cytomegalovirus

effectiveness against *C. albicans* endophthalmitis in rabbits [23, 24]. While voriconazole can achieve therapeutic concentrations in the vitreous when given systemically, it is important to note that posaconazole and the echinocandins do not and therefore have limited use in the systemic treatment route for fungal endophthalmitis [25].

3. Antiviral Agents

Acyclovir is an antiviral that is effective against the herpes family of viruses. It becomes activated in virus-infected cells by a virally encoded enzyme and is therefore nontoxic to uninfected cells. Ganciclovir is a nucleoside analog of acyclovir with 10–100-fold increased activity against cytomegalovirus (CMV). Intravitreal ganciclovir can be used safely at 2–5 mg even as often as every week, and low-volume weekly ganciclovir (1.0 mg/0.02 ml) after an induction treatment may be an alternative to sustained-release implants in the treatment of CMV retinitis [26]. Foscarnet is effective against herpes simplex virus, varicella zoster virus, and CMV. Intravitreal foscarnet can be given intravitreally at a dose of 2.4 mg without causing toxicity (Table IV.E-1). Cidofovir is a nucleoside analog that has a longer duration of action due to prolonged clearance compared to ganciclovir or foscarnet. However, it causes a high rate of uveitis (26 %) and hypotony, although these complications can be prevented by prophylactically treating with probenecid and topical steroid [27, 28].

4. Steroids

Triamcinolone acetonide (TA) was first used as an intravitreal injection by Machemer in the attempt to prevent proliferative vitreoretinopathy after retinal detachment repair [29]. It now has a variety of uses including the treatment of macular edema resulting from uveitis, diabetes, and retinal vein occlusion, as well as in pseudophakic cystoid macular edema (CME), radiation maculopathy, and CME related to retinitis pigmentosa (Table IV.E-2). In the treatment of macular edema following central retinal vein occlusion, patients treated with intravitreal triamcinolone acetonide (IVTA, 1 and 4 mg) were five times more likely to have a gain in visual acuity letter score of 15 or more letters at 1 year in comparison to observation alone [30, 31]. However, patients treated with 4 mg IVTA had higher rates of elevated IOP and cataract [30, 31]. Several studies have also shown that IVTA at doses of 2–4 mg is effective in the treatment of uveitic CME, but the effects of a single injection are temporary, lasting 3–7 months with a dose of 4 mg [32].

5. Anti-inflammatory/ Antineoplastic Agents

A prospective interventional case series reported on the use of intravitreal methotrexate in the treatment of uveitis and uveitic CME [33]. They found that 400 µg in 0.1 mL of methotrexate improved visual acuity over a 6-month follow-up period in 10 of 15 intermediate uveitis, panuveitis, or uveitic CME patients. No significant toxic effects were reported [33]. Intravitreal methotrexate has also been used for the treatment of vitreoretinal involvement in primary CNS lymphoma [34–36]. Complications in one series included cataract (73 %), corneal epitheliopathy (58 %), maculopathy (42 %), vitreous hemorrhage (8 %), optic atrophy (4 %), and sterile endophthalmitis (4 %) [37].

Table IV.E-2 Dosage and half-life of anti-inflammatory and anti-VEGF agents given intravitreally

Agent	Intravitreal dose	Half-life in vitreous	Clinical application
Anti-inflammatory			
Triamcinolone Acetonide	1–25 mg	For 4 mg dose: 18.6 days, non-vitrectomized 3.2 days, vitrectomized	Macular edema from uveitis, diabetes, vein occlusion, radiation, retinitis pigmentosa, pseudophakic CME
Methotrexate	400 µg	48 h	Uveitis, uveitic CME, intraocular lymphoma
Infliximab	1–2 mg	6.5 days	Neovascular AMD
Rituximab	1 mg	4.7 days	Intraocular lymphoma
Sirolimus	352 µg	NA	Noninfectious uveitis
Anti-VEGF			
Bevacizumab	1.25 mg	4.3 days	Neovascular AMD; macular edema in uveitis, diabetes, vein occlusion
Ranibizumab	0.5 mg	2.8 days	Same as above
Aflibercept	0.05–4 mg	4–5 days	Same as above
Pharmacologic Vitreolysis			
Ocriplasmin	125 µg	NA	Vitreomacular adhesion ± macular hole

CME cystoid macular edema, *AMD* age-related macular degeneration, *NA* not available [see chapter VI.E-1. Pharmacologic Vitreolysis with Ocriplasmin: Basic Science Studies]

Infliximab is a monoclonal antibody against tumor necrosis factor (TNF)-alpha used as a systemic treatment for rheumatologic conditions and the treatment of noninfectious ocular inflammatory disease. It has been applied at 1–2 mg doses intravitreally in the treatment of AMD [38–41]. After establishing a range of safe doses in an animal model, Theodossiadis et al. reported on three patients who received infliximab after failing to respond to intravitreal ranibizumab. All three patients had a reduction in central foveal thickness by optical coherence tomography as well as improvement in visual acuity [40]. Farvardin and colleagues described a decrease in mean central macular thickness and improvement in mean logMAR visual acuity after a single intravitreal injection of infliximab 1.5 mg/0.15 mL in ten eyes of seven patients who had refractory noninfectious uveitis, but the effects were temporary [42, 43]. Complications such as panuveitis and vitreous opacification after infliximab injection remain important concerns [42].

Adalimumab is a humanized antibody against the soluble and membrane-bound tumor necrosis factor (TNF), which has been studied for intravitreal injection in patients with uveitic CME but did not show improvement in vision or improvement in central macular thickness [44]. Rituximab, a humanized murine monoclonal antibody against the CD20 B-lymphocyte antigen used for the treatment of B cell lymphoma, is thought to be able to penetrate retinal tissue and has been studied for the treatment of intraocular lymphoma [45–47]. Santen Pharmaceutical is studying the efficacy and safety of intravitreally injected sirolimus, a T cell inhibitor that targets the intracellular protein mTOR (mammalian target of rapamycin), in a phase 3 study for the treatment of noninfectious posterior segment-involved uveitis (Table IV.E-2).

6. Anti-VEGF Agents

The anti-VEGF agents used for the treatment of neovascular AMD have revolutionized the use of intravitreal injections for posterior segment disease. Their use has since expanded to the treatment of macular edema due to diabetes, retinal vein occlusion, and uveitis. Ranibizumab is an Fab antibody fragment that binds to all isoforms of VEGF. Two large prospective, randomized controlled trials demonstrated the efficacy of ranibizumab in treating neovascular AMD compared to sham injections (MARINA), and when compared to PDT (ANCHOR), showing improvement in visual acuity in the anti-VEGF-treated patients [48, 49]. Bevacizumab (Avastin) is a full-length antibody against VEGF approved for systemic administration in the treatment of metastatic colorectal cancer. It has been used as an intravitreal injection for off-label treatment of neovascular AMD as well as for treatment of macular edema from retinal vein occlusion, diabetes, and uveitis. Two large trials, CATT and IVAN, have demonstrated lack of inferiority compared to ranibizumab at 24 and 12 months, respectively [50, 51]. The HORIZON study showed that long-term ranibizumab is well tolerated [52]. There have been concerns about higher rates of acute intraocular inflammation and outbreaks of infectious endophthalmitis for bevacizumab due to contamination during compounding into aliquots for intravitreal use [53, 54]. As mentioned in the complications section, several studies have also suggested a trend toward higher total systemic adverse events with bevacizumab compared to ranibizumab [16]. The use of ranibizumab has been expanded to the treatment of CME associated with retinal vein occlusions with improvements in visual acuity at 1 year in the BRAVO and CRUISE trials [55, 56]. Whether or not long-term repeated anti-VEGF

injections are required in vein occlusion patients with CME is a topic that requires further study.

Aflibercept is a chimeric fusion protein composed of an Fc fragment linked to the extracellular portions of VEGF receptors 1 and 2 that binds to all forms of VEGF as well as placental growth factor. The VIEW 1 and VIEW 2 studies demonstrated equivalency with monthly ranibizumab in maintaining vision at 1 year [57]. Additionally, the dosing regimen of 2 mg of aflibercept can be extended to every 2 months after the initial 3 monthly injections, decreasing the interval of monitoring and follow-up appointments. Ocular and systemic adverse events were similar between aflibercept and ranibizumab [57]. While aflibercept is FDA approved for use in AMD and CME related to CRVO, it is currently under active investigation for the treatment of diabetic macular edema (www.clinicaltrials.gov).

7. Pharmacologic Vitreolysis

Pharmacologic vitreolysis is a new treatment paradigm that can potentially replace vitreoretinal surgery for specific indications with pharmacotherapy [58, 59]. While several agents are under development [see references], the first to receive FDA and European approval is ocriplasmin (Jetrea®), a recombinant nonspecific protease [see chapter VI.E-1. Pharmacologic Vitreolysis with Ocriplasmin: Basic Science Studies and VI.E.2. Pharmacologic Vitreolysis with Ocriplasmin: Clinical Studies]. A single dose of 125 µg has been shown in phase III clinical trials to release vitreomacular adhesion and allowed for the nonsurgical closure of macular holes in 40.6 % vs. 10.6 % of placebo-injected eyes [60]. Additionally, there was improvement in best-corrected visual acuity of three or more lines in the ocriplasmin (12.3 %) group compared to placebo (6.4 %), $p=0.02$ [60]. Side effects were more common in the ocriplasmin group (68.4 % vs. 53.3 %, $p<0.001$) and most commonly included vitreous floaters, photopsia, eye pain, and subconjunctival hemorrhage [60]. Because of the pathological changes in the vitreoretinal interface found in diabetic retinopathy, this may be a condition that can be treated by pharmacologic vitreolysis, though further studies are warranted to determine whether this approach will be helpful [see chapters I.E. Diabetic vitreopathy; VI.A. Pharmacologic vitreolysis].

One limitation in the pharmacotherapeutic approach to vitreomacular disease is the lack of reproducible drug delivery to the site of interest, in this case the vitreomacular interface [see chapters II.E. Vitreo-retinal interface and inner limiting membrane; III.D. Vitreo-macular traction and holes (pseudo, lamellar and full thickness macular holes)]. Future developments should include improved drug delivery systems for pharmacologic vitreolysis. It is also plausible that combination therapy with more than one pharmacologic vitreolysis agent will yield better results [61].

B. Sustained-Release Drug Delivery

1. Implants

A shift from repeated intravitreal injections to sustained-release intraocular delivery devices in both implantable and injectable versions has recently occurred. These delivery devices can be classified into biodegradable and nonbiodegradable implants. The fluocinolone acetonide-releasing device or *Retisert* (Bausch & Lomb, Rochester, New York, USA), a nonbiodegradable steroid implant, has been FDA approved for the treatment of chronic, noninfectious posterior uveitis. It releases fluocinolone acetonide for approximately 30 months and is implanted through the pars plana through a scleral incision and secured using 8-0 Prolene suture (Figure IV.E-3a, d). In a 3-year clinical trial studying its efficacy in uveitis, Retisert was found by Callanan et al. to significantly reduce recurrences (from 62 to 4 %), and implanted eyes had improved visual acuity compared to non-implanted eyes ($p<0.01$) [62]. The MUST trial reported that after 24 months there was no statistical difference in visual acuity between systemic immunosuppression and the fluocinolone implant; it was successful in controlling 88 % of noninfectious uveitis [63]. Additionally, there was a higher rate of systemic complications with immunosuppression. On the other hand, ocular complications with the fluocinolone implant such as cataract (88–93 %) and glaucoma requiring surgery (21–40 %) [63, 64] limit its universal use and argue for combined cataract or glaucoma surgery in high-risk individuals [65]. Other reported side effects include hypotony, retinal detachment, endophthalmitis, and scleral thinning [62, 63].

Other sustained-release steroid-releasing implants that can be given through intravitreal injection in the clinic include a biodegradable dexamethasone implant (*Ozurdex*®, Allergan) (Figure IV.E-3c) and a nonbiodegradable fluocinolone acetonide insert (Iluvien®, Alimera Sciences) (Table IV.E-3). The advantage of biodegradable implants includes implantation without the need for extraction once drug elution terminates. However, biodegradable implants often have nonideal release kinetics and can have an uncontrolled burst of drug release at the end of their lifespan [1]. Nonbiodegradable implants, on the other hand, may require explantation once finished, but typically are longer lasting, and have closer to ideal drug-release kinetics (e.g., zero-order kinetics with Retisert, Figure IV.E-1). Ozurdex and Iluvien both have applicator systems that allow for outpatient placement through self-sealing, small gauge wounds (Figure IV.E-2, schematic). A phase III study that compared two doses (0.7 and 0.35 mg) of dexamethasone to sham treatment showed that both doses were effective in controlling inflammation and improving vision. However, the stronger dose had a longer duration of action and is now commercially available as Ozurdex. [66] While the incidences of

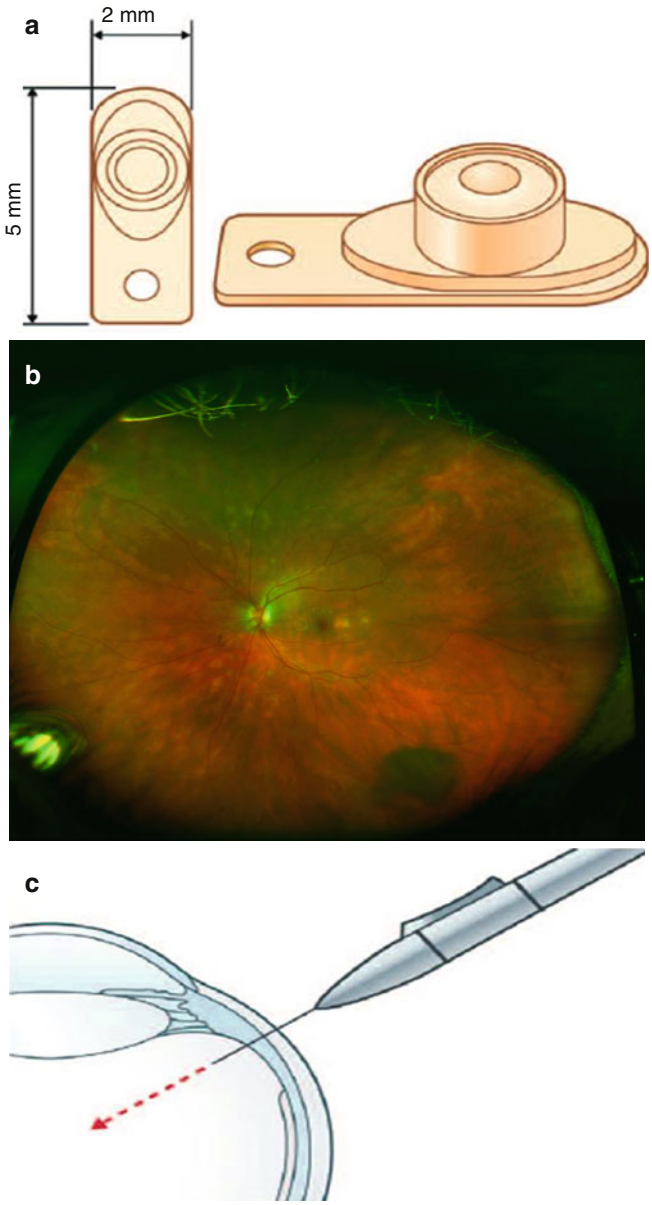

Figure IV.E-3 (**a**) Retisert® (Bausch & Lomb), fluocinolone acetonide, nonbiodegradable; (**b**) Retisert implanted into pars plana in patient with Birdshot chorioretinopathy; (**c**) Posurdex® (Allergan), now known as Ozurdex, dexamethasone ([93, 94])

cataract (26 %) and increased intraocular pressure were low, the effect of long-term use is unclear [66].

Iluvien is an injectable nonbiodegradable intravitreal insert that delivers sustained-release fluocinolone acetonide for 24–36 months at near zero-order kinetics. It is a 3.5 mm × 0.37 mm device that can be inserted in the office via a 25-gauge needle. The FAME study examined two doses of fluocinolone acetonide (0.5 µg/day vs. 0.2 µg/day) in patients with persistent diabetic macular edema despite one macular laser treatment. There was improvement in visual acuity by 1 month in comparison to controls, and this effect persisted through 36 months with 28.7 % (low dose) and 27.8 % (high-dose group) of patients maintaining an improvement of best-spectacle-corrected visual acuity of 15 letters or more in the two treatment groups [67, 68]. However, almost all patients required cataract surgery. Incisional glaucoma surgery was necessary more frequently in the high-dose group (8.1 % vs. 4.8 %) [67]. The Illuvien insert has been approved for use in diabetic macular edema in Europe. A fluocinolone acetonide insert (pSivida), similar to the Iluvien, lasts for up to 3 years after a single intravitreal injection and is currently undergoing phase I clinical trials for the treatment of noninfectious uveitis (www.clinicaltrials.gov).

The *Vitrasert*® implant is a polymeric (polyvinyl acetate) nonbiodegradable implant that releases 1 µg/h of ganciclovir with a duration of 8 months (Table IV.E-3). It was introduced in the 1990s to treat CMV retinitis in AIDS patients, but also has activity against herpes simplex virus. Studies have shown that the mean time to progression of CMV retinitis was 205 days with the ganciclovir implant which is approximately three times longer than with intravenous ganciclovir [69, 70]. The Vitrasert is no longer being produced and is not available for clinical use.

2. Encapsulated Cell Technology

Encapsulated cell technology is a method by which viable human cell lines that secrete a therapeutic protein are sequestered in a porous implant that allows for diffusion of the molecule out toward target tissues, while allowing for inward diffusion of oxygen and nutrients to maintain the health of live cells within the implant. This technology is being investigated for the treatment of retinitis pigmentosa and geographic atrophy (GA) in age-related macular degeneration.

Table IV.E-3 Intravitreal implants

Delivery system	Intravitreal dose released	Duration of action	Clinical application
Implants or inserts			
Retisert® (fluocinolone acetonide)	0.5 µg/day	30 months	Chronic noninfectious posterior segment uveitis
Iluvien® (fluocinolone acetonide)	0.2 or 0.5 µg/day	1.5 or 3 years	Same as above and CME due to RVO, uveitis, diabetes
Ozurdex® (dexamethasone; biodegradable)	350 or 700 µg	6 months	Same as above
[a]Vitrasert®(ganciclovir)	1 µg/h	8 months	CMV, HSV, VZV

RVO retinal vein occlusion
[a]No longer available

The NT-501 Neurotech implant consists of a semipermeable outer membrane with 15 nm pores that allows for growth factors and oxygen to reach viable human retinal pigment epithelial cells that have been engineered to secrete ciliary neurotrophic factor (CNTF). This RPE cell line is maintained on a polyethylene terephthalate yarn scaffold inside the implant. The NT-501 implant is placed into the eye through a 2 mm incision through the pars plana. CNTF is a cytokine that binds to receptors found on Muller glial cells, rods, and cone photoreceptors [71]. It has been demonstrated to retard photoreceptor degeneration in animal models of retinitis pigmentosa [72]. Phase II data for the use of the CNTF implant for GA suggest dose-dependent changes in retinal thickness that is followed by visual stabilization in the high-dose group (96.3 %) and low-dose group (83.3 %) compared to the sham group (75 %) [73]. For retinitis pigmentosa, phase I study results have been published reporting three of seven implanted eyes that could be tracked by conventional reading charts with an improvement in acuity of 10–15 letters [74]. There were no serious complications in the ten eyes that were implanted. Neurotech has also developed encapsulated cell technology which has been designed with a cell line engineered to release a VEGF receptor Fc-fusion protein. This construct is 20-fold more efficient in neutralizing VEGF than ranibizumab, releases the fusion protein for up to 1 year in the rabbit vitreous, and is undergoing a phase 1 clinical trial for neovascular AMD outside of the United States (www.clinicaltrials.gov).

3. Microspheres

The concept of microspheres is to use biodegradable polymers such as polylactide and poly lactic-co-glycolic acid (PLGA) to suspend drugs into microparticles (1–1,000 μm) or nanoparticles (1–1,000 nm) resulting in controlled release of drugs [1]. They provide sustained drug release for weeks to months. Their advantage is that drug is released in a controlled fashion, minimizing the "burst" effect that biodegradable implants have at the end of their lifespan. Microspheres are injected into the vitreous cavity, and thus, the disadvantages are synonymous with the complication rates associated with any other intravitreal injection although drugs delivered in this method would need to be injected much less frequently. An additional complication is that nanoparticles may cause temporary clouding of the ocular media, although microspheres larger than 2 μm circumvent this problem because they sink to the bottom of the vitreous cavity due to gravity. However, head and body movement may cause upward displacement of the microspheres, blurring vision. This technology has been used to incorporate the pegylated anti-VEGF peptide, pegaptanib, into a vehicle that, when applied using a transscleral technique, released drug for up to 20 days, resulting in inhibition of VEGF-induced cell proliferation of human umbilical vein endothelial cells [75]. Cardillo et al. demonstrated in their case series that a microsphere preparation of triamcinolone acetonide was effective in reducing foveal thickness and improving visual acuity in patients with diabetic macular edema when compared to the conventional preparation of triamcinolone [76]. Microspheres may have a shorter half-life in eyes that have undergone vitrectomy.

4. Porous Silicon Particles

Micro-particulate photonic crystals made from porous silicon particles are now being studied as an intraocular sustained-release drug delivery system. The drug is chemically attached to the inner pores of the microparticle and released as the matrix dissolves. A recent *in vivo* study of covalently loaded daunorubicin, an antiproliferation medication with a short vitreous half-life formulated in oxidized porous silicon for the treatment of proliferative vitreoretinopathy, appears to be promising, with no toxicity at 6 months [77]. The microparticles were, on average, 30×46×15 μm with a pore size of 15 nm and a reddish color that decreased as the matrix degraded and daunorubicin was released [77]. Long-term and human studies are still required to establish efficacy and safety.

5. Liposomes

Liposomes are lipid vesicles made of phospholipids 25–10,000 nm in diameter that can be used to encapsulate both hydrophilic (in the core) and lipophilic (between the bilayer) drugs. They undergo phagocytosis by retinal pigment epithelial cells, thus allowing for targeted intracellular drug delivery. This technology has been utilized to create less toxic formulations of amphotericin B and gentamicin in animal models, although their utility in human intraocular disease is limited [78, 79]. Liposomes designed to release vasoactive intestinal peptide appear to have an anti-inflammatory effect in rats with endotoxin-induced uveitis [80]. Bevacizumab encapsulated into liposomes achieved higher concentrations in the rabbit vitreous at 28 and 42 days compared to soluble bevacizumab, although toxicity studies have not yet been conducted [81].

6. Suprachoroidal Microinjection and Microneedles

Microcannulation of drug delivery devices into the suprachoroidal space is a promising new technique that can potentially directly deliver drug to the macula, optic nerve, and posterior pole [82]. Advantages of this technique include higher drug levels to target tissues and decreased unintended exposure to nontarget tissues, which could decrease the incidence of cataract and increased IOP. One study used microneedles to inject the suprachoroidal space of rabbit eyes with fluorescently tagged dextrans and particles from 20 nm to 10 μm in size [83]. Patel et al. found that smaller molecules were cleared in hours, whereas suspensions of

nano- and microparticles remained in the suprachoroidal space for months [83]. Further research is required to improve access to the suprachoroidal space and study this system in human eyes. Phase 2 clinical trials for a microneedle device used to inject triamcinolone acetonide into the suprachoroidal space for the treatment of noninfectious uveitis affecting the posterior segment are underway.

V. Future Drug Delivery Approaches and Considerations

A. Iontophoresis

Iontophoresis is a nonsurgical technique that utilizes an applicator to deliver a weak electrical current to the sclera to drive ionically charged drug molecules across the sclera into the choroid, retina, and vitreous [84, 85]. This technique shows future promise for the delivery of sustained-release formulations with the ability to modulate dosage by altering the strength of current utilized. One study showed successful delivery of triamcinolone acetonide and ranibizumab through full-thickness rabbit ocular tissue [86]. Phase 2 clinical studies investigating the use of iontophoresis of dexamethasone phosphate for the treatment of anterior uveitis have been completed, and studies for this modality in the treatment of noninfectious non-necrotizing anterior scleritis are underway.

B. Refillable Delivery Systems

Refillable port-delivery systems (PDS, ForSight VISION4, Inc.) implemented by Genentech for delivery of ranibizumab may decrease the need for repeated intravitreal injections for wet AMD. The PDS is implanted surgically into the pars plana without scleral sutures and loaded with ranibizumab. Phase 1 data presented at the 2012 AAO meeting showed proof of concept for sustained release of ranibizumab with the PDS. At 12 months, most patients achieved significant gains in visual acuity from baseline, and 50 % gained 3 lines or more. Examination of devices explanted per protocol at 12 months, and observation of devices that remained in patients at month 36, indicated ongoing integrity and tolerability of the device. Alternatively, the microelectromechanical systems (MEMS) delivery device is a subconjunctival reservoir that forces drug through a cannula inserted into the anterior or posterior segment.

C. Advances in Sustained-Release Intravitreal Injectables

Tethadur (pSivida) is a nanostructured porous silicon microparticle that can be designed to release various peptides, chemical molecules, therapeutic antibodies, and proteins in a sustained fashion. De Kozak et al. have used cyanoacrylate nanoparticles coated with polyethylene glycol to release tamoxifen to reduce inflammation in a rat model of uveitis [87]. The *Verisome* system (Icon Bioscience, Sunnyvale, CA) is an intravitreally injected liquid or viscous gel that is biodegradable and can be formulated to release small molecules, peptides, proteins, and monoclonal antibodies [87]. When injected via a 30-gauge needle into the vitreous cavity, it forms a spherule that can be assessed visually to monitor duration of action. A Verisome spherule designed to release a combination of triamcinolone and ranibizumab is being studied in phase 2 clinical trials for the treatment of neovascular AMD. It is expected to release drug for up to 1 year (www.clinicaltrials.gov). The *Cortiject* emulsion (NOVAA63035, Novagali, Pharma) is given as an intravitreal injection that provides sustained release of corticosteroid for 6–9 months. This is being tested in phase 1 studies for the treatment of diabetic macular edema, but has not yet been tested in uveitis.

D. Emerging Methods for Local Delivery

Small interfering RNA (siRNA) and microRNA technology can be designed to inhibit the expression of inflammatory cytokines. A phase 2 study of siRNA technology to treat AMD was terminated due to a company decision perhaps related to lower efficacy than ranibizumab. Other strategies such as designing viral vectors to sustain expression of antibodies that block inflammatory cytokines have yet to be fully developed but may represent an alternative sustained delivery method. Additionally, nonviral gene transfer techniques can be devised to deliver therapeutics to the eye. Behar-Cohen and colleagues have developed a recombinant protein ocular delivery system that utilizes an electrical current to transfer a plasmid encoding a soluble chimeric TNFα receptor directly to the ciliary muscle. This has achieved sustained local protein production for up to 3 months after introduction and appears to inhibit rat endotoxin-induced uveitis [88].

E. Vitreous Structure and Intravitreal Drug Delivery

It is important that all intravitreal drug delivery approaches take into consideration that vitreous is not a space or cavity, but a living tissue. Thus, except in the case of eyes that have undergone vitrectomy, all calculations of the pharmacokinetics of intravitreal drug therapy must be based on a more realistic approach than just assuming first-order kinetics. This consideration is further complicated by the fact that the molecular composition of vitreous changes with age [see chapters I.A. Vitreous proteins; I.F. Vitreous biochemistry

and artificial vitreous; II.C. Vitreous aging and PVD], refractive state [see chapter II.B. Myopic vitreopathy], and systemic disease such as diabetes [see chapter I.E. Diabetic vitreopathy]. Drug distribution following intravitreal administration *cannot* be the same in all of these circumstances, and there are many more such settings that are currently not receiving enough consideration. Furthermore, the particular site of injection will influence pharmacokinetics because vitreous structure is quite heterogeneous within the vitreous body, except in very young children. The heterogeneity of vitreous structure increases with age [89, 90] and different disease states, especially diabetes [91, 92]. That an injection into different locations within the vitreous body can have very different pharmacokinetics is considered elsewhere in this text [see chapter VI.A. Pharmacologic vitreolysis].

Abbreviations

AMD	Age-related macular degeneration
CME	Cystoid macular edema
CMV	Cytomegalovirus
CNS	Central nervous system
CNTF	Ciliary neurotrophic factor
CRVO	Central retinal vein occlusion
FDA	Food and Drug Administration
GA	Geographic atrophy
IOP	Intraocular pressure
IVTA	Intravitreal triamcinolone
PDS	Port-delivery system
PDT	Photodynamic therapy
PLGA	Poly lactic-co-glycolic acid
RPE	Retinal pigment epithelium
TA	Triamcinolone
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor

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