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► To cite this version:

Francine Behar-Cohen. Recent advances in slow and sustained drug release for retina drug delivery. Expert Opinion on Drug Delivery, 2019, 16 (7), pp.679-686. 10.1080/17425247.2019.1618829 . hal-02361158

HAL Id: hal-02361158

<https://hal.sorbonne-universite.fr/hal-02361158>

Submitted on 29 Jun 2020

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Recent advances in slow and sustained drug release for retina drug delivery

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Highlights:

- Drug delivery remains a major challenge in the treatment of retinal diseases
- Degradable and non-degradable implants for the sustained and local release of glucocorticoids have been approved
- Bolus of proteins neutralizing VEGF family members allow the maintenance of clinical benefit for 1 to 3 months
- New reservoirs and polymeric dispersed systems are in development for intravitreal slow release of drugs and proteins
- Few drug delivery systems cross the clinical stage due to insufficient multidisciplinary development
- Fundamental work is still required to build guidelines for toxicity and models for ocular pharmacokinetic studies.

Key words:

Ocular pharmacokinetics, drug delivery, retina, therapeutic proteins, vitreal implants, polymers, nanosystems

Abstract

Introduction

Striking recent advance has occurred in the field of medical retina, greatly because intraocular drugs have been developed, enhancing their clinical efficacy while avoiding systemic side-effects. But, the burden of repeated intraocular administration makes limits the optimal efficacy of treatments, prompting the development of new drugs with prolonged half-life or of sustained drug delivery systems.

Area covered

In this review, we describe the various drugs and drug delivery systems that have reached the clinical stage and those that are in clinical development and we discuss the limitations to clinical translation.

Expert opinion

Substantial fundamental work is still required to build guidelines on optimal animal models for ocular pharmacokinetics and safety studies depending on the target disease site and the on the type of therapeutic compounds. The effects of a drug administered as a bolus at high concentration in the vitreous might differ from those resulting from the sustained release of a lower concentration, and no delivery platform can be simply adapted to any drug. For the treatment of retinal diseases, development of therapeutic compounds should integrate from its early conception, the combination of an active drug with a specific drug delivery system, administered by a specific route.

Retinal diseases remain the main causes of visual impairment in industrialized countries due to population aging and to the high prevalence of diabetes and of myopia[1,2]. Major therapeutic advances have been achieved in the last 15 years in the field of retinal diseases allowing not only to stabilize vision of patients presenting macular edema of various origins including diabetic retinopathy, choroidal neovascularization secondary to age-related macular degeneration or to myopia, and to retinal vein occlusion, but also to reach clinically significant vision gain using repeated intraocular administration of either anti-angiogenic recombinant proteins[3-6] or different glucocorticoids formulations[7-9]. These therapies reduce macular edema [10] but they do not cure the disease explaining that the symptoms recur when the drug reaches the lowest efficacy threshold. Whilst curative therapies remain to be discovered, tremendous efforts are being made to prolong the beneficial anti-edematous effects of the actual drugs in order to reduce the frequency of intraocular administrations. Indeed, all real-life studies have shown that the visual benefit is not as good as in randomized controlled trials due to poor compliance and to the burden of repeated intraocular injections[11-14].

On the other hand, to target neurodegenerative processes and delay photoreceptor loss that progresses over decades, any potential drug should be formulated in a way that limits the number of administrations over years. Moreover, there are many potential drugs, targeting pathogenic mechanisms in the retina, that either do not cross the blood retinal barrier and/ or have a very short-half-life when injected into the vitreous preventing them from being selected as potential retinal drug candidates.

Drug delivery to the posterior segment of the eye thus remains one of the major challenges in the treatment of retinal diseases. Indeed, the eye is an ideal organ for the local delivery of active principle. It is a small organ containing different cavities filled with fluids, directly accessible using minimally or eventually non-invasive methods. In this review, we will summarize different strategic approaches that have been envisaged for delivering drugs, proteins or small molecules to the back of the eye, emphasizing on those that have reached the clinical stage.

1. General considerations

When designing drug delivery for the treatment of retinal diseases, several essential questions must be answered regarding the target site and the drug:

- What is the target tissue or cell?

The retina is in direct contact with the vitreous cavity, but the active principle might not diffuse freely from the vitreous to the different layers of cells in the neuroretina, or to the retinal pigment epithelium (RPE) and to the choroid (Figure 1). Indeed, there are molecular barriers at the inner limiting membrane, the outer limiting membrane and at the RPE[10,15-17]. The bioavailability of a molecule into the retina is also governed by endogenous molecular gradients and by active transports and efflux proteins[18-20].[21]. The optimal route of administration and the target concentration in the vitreous might differ if the target is in the superficial retinal layers, the outer neuroretina or in the choroid (Figure 1). The choice of the route of administration should thus be guided by the pathogenic mechanism site.

- What is the most relevant model to perform pharmacokinetic and biological efficacy studies?

Except from non-human primates which also have a macula, no animal model recapitulates fully the distribution of drugs into the macula, which is the site of most diseases (AMD, diabetic macular edema, vascular-induced macular edema, choroidal neovascularization.). Not only is the use of monkey limited by ethical and cost, but monkey eyes are smaller than human eyes and their macula also differs from the human one. In addition, research is still needed to establish whether drug penetration and distribution in the avascular macula differs from the other parts of the retina. Rabbits are thus often used for pharmacokinetic studies because the size of the rabbit eye is closer to the human eye and although the vitreous volume is much smaller, it is cheaper and seems to be a predictable model[22]. But, since few retinal disease models are relevant in rabbit as compared to rodents, biological efficacy is often evaluated in rodents, in which pharmacokinetic studies are difficult and poorly relevant to humans. Therefore, several animal models are used, each one for a specific and complimentary aims and correlation between pharmacokinetic and pharmacodynamic effects can rarely be established. Human

pharmacokinetics are obviously the most valuable data as they can be correlated to clinical efficacy but in humans only the aqueous humor can be repeatedly sampled. A complex modeling is thus required, based on many hypotheses, to extrapolate retina or even choroid drug concentration from the aqueous levels [23-25]. When developing therapeutic proteins, immunologic reactions against human proteins are expected in animal including eventually monkey, resulting in low predictability of animal pharmacokinetics to human. There is no universal and optimal animal model to study ocular pharmacokinetic and a strategic plan must be drawn depending on the route of administration the type of drug delivery system, and the drug, to overcome technical issues and often, several complementary animal models are required.

- What is the target concentration? in which compartment should it be measured?

These questions are crucial when designing a drug delivery system. The target drug concentration in the vitreous might not be simply extrapolated from preclinical *in vitro* or *ex vivo* assays. In example, the anti-VEGF ranibizumab inhibits proliferation of endothelial cells *in vitro* with an average IC₅₀ value of $0.088 \pm 0.032\text{nM}$ [26], which would correspond to less than 10 pg/ml in the vitreous, but according to pharmacokinetic/ pharmacodynamic models, that take into account the diffusion of the drug in the retina and the correlation between reduction macular edema and the minimal efficient ranibizumab concentration in human vitreous is around 0.1µg/ml [23,24]. Indeed, once administrated in the vitreous, the injected drug may bind to various molecules, diffuse in compartments where it can be eliminated, metabolized or sequestered and then slowly released, it may diffuse or be actively transported to the retinal layers and eventually to the RPE/ choroid and, its biological effect can result from indirect mechanisms at a site which is different from the pathologic site[24]. In the case of anti-VEGF proteins, these large molecules are mostly eliminated via the aqueous outflow and the fraction of drugs that finally reaches the retina and the choroid, where choroidal neovascularization develops in the case of AMD, is limited by the permeability coefficients between retina and vitreous and between retina and choroid[24]. Moreover, how the anti-VEGF exert their anti-edematous effects in various ocular

diseases, in which many other pro-angiogenic and pro-permeating cytokines are produced remains imperfectly understood. Finally, the biologic effects observed when a bolus of drug is injected into the vitreous can result from complex mechanisms, including change in oncotic pressure in the vitreous when proteins are injected, off-target effects due to the high concentration of active principle, or cell membrane destabilization due to hydrophobic compounds. The difficulty in predicting efficient drug concentrations in one measurable compartment, explains that the duration of clinical effects in humans may differ from pharmacokinetic predictions. Variations amongst individuals is also frequently observed justifying a personalized regimen of injections[27]. It is expected that with accumulating data from human subjects and from pharmacokinetic/ pharmacodynamic modelling, the prediction might improve [25].

2. Specific requirements for the delivery of therapeutic proteins or for small molecules

Therapeutic proteins or peptides have poor retinal biodisponibility when administered systemically, although it can be enhanced in pathological conditions that alter the blood retinal barriers such as in intraocular inflammation (non-infectious uveitis or endophthalmitis). Humira has been recently approved using systemic route for the treatment of uveitis[28] but whether the drug acts through direct neutralization of ocular TNF- α remains to be demonstrated. In other conditions such as diabetic retinopathy, age-related macular degeneration, retinal vein occlusions, and other forms of macular edema of any origin, anti-angiogenic proteins, with half-life of several days, are administered into the vitreous at frequency varying from monthly to bi-monthly. High doses are directly injected in the vitreous to maintain a high enough concentration for at least 21 days. Any attempt to encapsulate therapeutic proteins into polymers, reservoirs, particulate systems must consider its stability at body temperature, and the loading limitations due to the high size of the molecules. Smaller sized proteins such as single chain antibodies might be better candidates for polymeric encapsulation and, chemical modifications to stabilize the proteins might be required. Six milligrams of a 26KD single chain antibody neutralizing VEGF, injected in the vitreous has recently shown potential for an extent anti-edematous duration in AMD[29].

For small molecules, half-life is usually much shorter, particularly for hydrophilic molecules that are rapidly cleared through the aqueous humor pathway or through the retina. More than 15 years ago, the very low soluble injectable triamcinolone acetonide formulation has been injected off label into the vitreous as solid crystals in suspension in various excipients, acting as an uncontrolled drug reservoir[30], with potential retinal toxicity[31]. Since then, approved ocular formulations for intravitreal injection of triamcinolone acetonide, in which the size of particles has been controlled and the toxic excipient removed have been developed[32]. Although not a sophisticated formulation, it does provide at least 3 months of efficacy in the reduction of macular edema[32]. Except from such hydrophobic compounds that can be formulated as suspension or crystals, to achieve several months of efficacy, small molecules must be delivered in a slow release system to avoid frequent re-injections, either into the eye or in various spaces around the eye. To be adopted by clinicians, a drug should optimally be injected every 2 to 6 months to reduce the burden of injection and of follow-ups.

3. The routes of administration

Figure 1 summarizes the different routes that have been used to deliver drugs for the treatment of retinal diseases. Although topical drops have been considered as poorly efficient to deliver efficient levels of drugs to the retina, new formulations made of nanocarriers, that enhances the penetration inside cells of the ocular surface tissues, that then act as reservoirs, might be able to favor the transscleral route and subsequent delivery of small molecules to the more external tissues of the posterior segment [33,34]. Various drops of lipid nanoparticles, liposomes, emulsions (cationic or anionic), polymeric micelles, polymeric nanoparticles, dendrimers, cyclodextrins micelles have been developed and tested in various animal models [35]. Caution should be made when interpreting pharmacokinetic results as regional anterior concentration can mask a poor bioavailability of the drug in the posterior region of the retina, where the macula is located. A cyclodextrin microparticle drop delivering dexamethasone is being tested for the treatment of diabetic macular edema[36,37] [Oculis, Switzerland]. Results of the Oculis study is expected as previous attempts to deliver anti-inflammatory drugs, either steroids [FOV2304, NCT01319487] or NAIDS did not show positive results

[38]. If positive results are achieved, it will open the field for many other topical drops for retinal diseases.

Peri-ocular injections are frequently used in clinical practice, based on empiric experience as very limited pharmacokinetic data in humans are available to support and favor one or the other routes to treat diseases of the posterior segment [39-41]. Sub-conjunctival, sub-tenon, peribulbar and retrobulbar injections are performed. Recent studies comparing sub-tenon injection of triamcinolone acetonide with intravitreal dexamethasone implants for the treatment of uveitis have concluded that intraocular administration was more efficient and lasted longer [42]. More interesting is the comparison of triamcinolone administered either into the vitreous or injected sub-tenon for the treatment of uveitic macular edema, which also showed that intraocular administration was more efficient, although associated with higher intraocular pressure complications [43], demonstrating that the direct delivery of drugs, that target almost all retinal cells, like corticosteroids, benefit from a direct intravitreal administration. In addition, periocular injections expose to systemic drug exposure and associated potential side effects.

Intravitreal administration is the most frequently used route for therapeutic proteins as well as for small molecules (glucocorticoids, antibiotics, anti-VEGFs...). This route has been adopted with the development of new drugs for the back of the eye. Indeed, limited to rare cases of retinitis and endophthalmitis twenty years ago, the number of intravitreal injection has reached 5M in the US in 2016 and continues to rise[44]. But injecting the drug inside the vitreous does not imply that the drug reaches its target tissue or cell, or that an efficient concentration is maintained depending on the drug but also on ocular factors and individual variations, that still remain to be understood[45-47]. Yet, the vitreous cavity is an ideal space to insert any type of solid, semi-solid or particulate drug delivery systems; either degradable or non-biodegradable. The injected or surgically inserted material, containing drugs, can be monitored visually and can be positioned away from the visual axis to limit visual burden.

Suprachoroidal delivery has been described almost 50 years ago[48] but was disregarded until our group described in 2002 the suprachoroidal injection of a semi-solid poly(ortho)ester biodegradable material, that was showed to diffuse

towards the posterior segment when injected at the pars plana [49]. More recently, the microneedle technology has been developed to inject in a controlled manner, drugs into the suprachoroidal space, in order to position the drug closer to the targeted tissues as compared to the periorbital injections. Lower but more targeted doses of triamcinolone acetonide could lead to similar efficacy but reduced side-effects[50],[51]. This technology is developed by Clearside for the treatment of diabetic macular edema, macular edema secondary to uveitis [52], or to vein occlusion [53]. It is important to consider the clearance mechanisms for each specific drug and each route of administration, as elimination of the drug through the anterior aqueous humor pathway, the retinal pathway, or through the retinal vessels, target to efflux proteins, degradation mechanisms, influence the effectiveness of drug delivery system[23,25,54]

Sub-retinal injections directly target the RPE and the photoreceptor cells, but except when the retina is already detached, this route of administration is associated with significant risks and is highly invasive. It is now restricted to the administration of viral vectors for gene therapy [55,56] or to the injection of cells.

4. Biodegradable polymers

The list of biodegradable polymers that can be used for the sustained release of drugs to the posterior segment of the eye and that have been used in the preclinical stage is long (Synthetic polymers, such as poly(amides), poly(amino acids), poly(alkyl-a-cyano acrylates), poly(esters), poly(orthoesters), poly(urethanes), and poly(acrylamides)...), but the number of polymer that have been used in human is very short. Indeed, the clinical use is limited by the need to evaluate not only the safety of the polymer itself but also the safety of all its bioproducts, that are not always even characterized. As compared to other tissues, the retina is a direct prolongation of the brain, in which cells are post mitotic and very sensitive to any metabolic changes. Any injury to the retina might cause irreversible vision loss. In addition, the vitreous being acellular and directly accessible to observation, any modest inflammatory reaction, that could have been tolerated elsewhere in the body, is not acceptable for eye application. Another constrain is the fact that fluid in the vitreous has a low rate of renewal, exposing

to change in pH or in the accumulation of toxic degradation products. To overcome this problem, the amount of polymer injected in the vitreous should remain limited to allow dilution of acid degradation products. The tolerance of polymers per se is not of much interest as a product is the combination of polymer with a specific drug, in a specific solid or semi-solid state at a certain concentration ratio of drug/polymer. It is not possible to extrapolate simply what will be the tolerance of a specific polymeric / drug formulation, but known polymers are usually preferred to limit the preclinical toxicology package required to enter into clinical phases.

The polymers most commonly used in biodegradable delivery systems are thermoplastic aliphatic poly(esters) of the poly- α -hydroxy acid family including polylactic acid, polyglycolic acid (PLGA), and polylactic-co-glycolic acid. These polymers are well known and widely used in medicine including in the field of ophthalmology for sutures. These polymers are non-toxic except if high amount of polymer degrading in lactic acid causes acidification of the microenvironment and subsequent inflammatory response. Manufacturing processes can include solvents that should be carefully removed in order to limit any undesirable toxicity. To date, the only biodegradable implant approved for the treatment of diseases affecting the back of the eye is Ozurdex®, a dexamethasone phosphate (700 μ g) loaded PLGA (50:50) rod, inserted into the vitreous through a proprietary injector. [It releases dexamethasone for up to 6 months, but depending on the disease and the individual patients' condition, the threshold glucocorticoids concentration needed to control the inflammatory signs may vary, requiring more frequent injections \[8,57-59\].](#) Because dexamethasone is a potent anti-inflammatory drug it does not allow to evaluate a potential pro-inflammatory effect of the polymer itself. In addition, polymer residues can persist while the drug release is complete. As expected with this type of polymer, initial and late phase bursts are observed. Other polymers, such as poly(ortho)esters have been evaluated for ocular applications. They offer the advantage of being semi-solid and injectable through small gage needle and are extremely well tolerated while releasing drugs for several months with a zero kinetic order. In addition, the rate of degradation can be modulated by pH modulation. Viscous injectable Poly(ortho)esters have been evaluated for intravitreal and suprachoroidal delivery[49,60]. No further clinical development was made due to manufacturing and up-scaling issues. Poly- ϵ -

caprolactone (PCL) has also been widely studied as it allows a very long-term release of drug into the vitreous and is very well tolerated in contact with retinal cells. After several months in the vitreous, this very hydrophobic material degrades into fragments, and eventually degradation can be too slow, leaving material into the eye. Electro spun nanofibers of PCL might solve this later issue[61-63]. Peggulation and co-polymerization is often performed to reduce inflammation, prolong the duration of release and change the solid state of the polymers. There is indeed a particular interest in hydrogels, such as those made of co-polymers like the InGel® from Innocore, based on PCLA-PEG-PCLA tri-block copolymers with aliphatic end groups that are injectable and can be thermos-sensitive. Shape memory materials should also take an important place in the field of ocular delivery allowing to enroll in the vitreous cavity an enhanced length the material, increasing its loading capacity and release duration [64,65] . Other materials can be used, such as polyethyleneimine (PEI), particularly adapted to formulate nucleic acids such as antisense oligonucleotides or siRNA[66-68]. They can form particulate system with high transfection capacity in retinal cells[69,70]. As siRNA particulate system get approval for the treatment of systemic genetic diseases, it is expected that such a strategy will become possible for the treatment of hereditary eye diseases[71]. Cyclodextrins are also widely used to form Nano micelles, that eventually could target the retina and the choroid after topical instillation, as developed by Oculis (SA, Switzerland) [36,37].

5. Particulate systems, solid implants or hydrogels

As mentioned previously, degradable material can be used to form nano or microparticulate systems (particles, micelles, spheres...)[72], solid, semi-solid, viscous, or gel for the release of drugs[73]. [Each drug delivery system carries advantages and potential drawbacks and the shape and form of the system, using a same biomaterial, might result in different tolerance\[74\], which also can vary depending on the injection or implantation site. Solid injectable implants, biodegradable or not are already approved for the slow release of glucocorticoids into the vitreous\[57,75\]. Particulate systems and hydrogels are being tested in clinical trials to deliver small molecules \[NCT/03630315\].](#)

To treat a posterior segment disease, the optimal drug delivery system should fulfill the following requirements. It should be injectable through a small gauge needle (26-30 gauge) or applied topically, under no or topical anesthesia for a good tolerance, particularly if repetition is needed. It should not cause visual disturbance for a prolonged duration after injection. This might be taken into consideration when particulate systems are injected into the vitreous as they may be visible by the patients as myodesopsia. The drug delivery system should be biodegraded to avoid the need to removal when it is empty or its remanence in the eye for an undetermined period of time. It should release drugs or proteins for a sustained period of time with a zero kinetic order and should degrade completely when no drug is left. The system must be non-toxic, and the degradation products should be known and safe for the ocular tissues. This is particularly important when new polymers are used. Limited and controlled changes in the ocular media chemical composition is preferable to limit potential toxicity and ensure the drug stability (i.e. acidification). For further clinical development, the system must be manufactured and upscaled and sterilized and the product need to be reproducible and stable with time.

6. Non-biodegradable materials

Non-biodegradable polymeric implants can present in the form of matrix (monolithic) or reservoir systems, eventually refillable. Slow and controlled diffusion of the drug contained in the reservoir is achieved by diffusion through a polymeric membrane. The drug-release rate is determined by the release area, the thickness of the polymeric membrane, as well as drug solubility. Silicon, polyvinyl alcohol (PVA) and ethylene vinyl acetate (EVA) are the most used polymers[76]. Non-biodegradable implant containing fluocinolone acetonide, Illuvien® (Allimera Sciences) has been approved for the treatment of severe forms of diabetic macular edema. It allows a stable drug release for at least two years[77-79]. Illuvien® is a miniaturized and injectable version of Retisert® which was surgically implanted and was associated with a high rate of dissociation [80], [81]. The Illuvien® implant has demonstrated its safety and offers a long and controlled release of drug but its cost is high, and the empty implant stays inside the vitreous cavity. For the sustained delivery of proteins, Genentech, Inc, USA, has developed a non-

biodegradable, refillable, implantable reservoir, that is surgically inserted in the sclera. It seems to be able to extend the duration of the anti-VEGF, ranibizumab up to 6 months [82].

7. The gene therapy approach

For the slow release of proteins, a direct local production is an attractive strategy. It allows permanent local production of therapeutically active proteins, produced by the ocular cells, that perform endogenous post transcriptional modifications. Viral vectors are proposed to transduce either retinal pigmented epithelial cells through invasive sub retinal delivery, or glial Müller cells through intravitreal injections[82,83]. There is no exit strategy, the protein could continue to be secreted for an undetermined duration, exposing to over-dosage and undesirable side-effects. Another strategy proposes to transduce the ciliary muscle cells, that are non-retinal and non-visual cells, using a non-viral gene delivery, mediated by electrotransfer. The production might last for 6 to 9 months, as the plasmid, remaining episomal, is silenced after several months. Repetition is possible and the technique is minimally invasive[15,84]. For the regulation of cytokines and growth factors, this approach seems promising. Both strategies have entered the clinical development stages. For the replacement a mutated gene, viral gene therapy is the method of choice allowing to deliver the missing gene, that theoretically should be expressed for a lifetime. One product has been approved for the treatment of retinitis pigmentosa associated with mutation in RPE65 gene (Voretigene neparvovec, Luxturna ® Novartis). The long-term results seem to show that the expression might not be stable in all cases and that the treatment might be able to stop the disease progression only in a subset of patients[85]·[86]. Nevertheless, this has been a real breakthrough in the field, although the very high pricing of this first gene therapy can be a limitation[87]·[88].

8. Expert opinion

The eye is the ideal organ for local drug delivery. The ocular barriers prevent drug penetration from the circulation but also retain the drug inside the eye allowing a real local treatment with no significant systemic side-effects. Easily accessible, the eye can be targeted by many routes but the more direct is the intravitreal

administration of various formulations, polymeric material, forming implants, particulate systems, nanofibers, hydrogels....Most of the systems seem safe in preclinical testing, they are efficient in various models of eye diseases, but they are not developed for further clinical applications. Reasons for this low rate of transformation from preclinical to clinical development are multiple. Inadequate models for testing the safety and pharmacokinetics lead to non-transposable results in non-human primates or in humans, the preparation method at the scale of an academic laboratory might not be scalable for industrialized purposes, sterilization methods might alter the polymeric formulations. But most importantly, the development of drug delivery systems for a specific organ requires that scientists from multiple fields collaborate and bring the project up to the clinical stage, knowing all the regulatory, manufacturing and medical issues.

What will be next? Drug delivery systems that have been evaluated since years will finally cross the line of the clinical study, particularly the particulate systems (nano-micelles, microparticles....) and the thermosensitive hydrogels. Combination of complex surgical procedures with drug delivery systems allowing to improve the visual outcomes of surgery and the local and targeted delivery of drugs and proteins should be envisaged. Combination of chemical methods with physical methods to activate locally the release of drug using light, ultrasound should be better explored through multidisciplinary collaborations. With improved delivery methods, many known drugs could be repurposed for the treatment of retinal diseases. The actual generation of ophthalmologist have witnessed tremendous improvements in the treatment of retinal diseases through the local delivery of repurposed drugs (anti-VEGF used for cancer, glucocorticoids...). Such success has prompted pharmaceutical industry to consider ophthalmology and more specifically the retina as a priority, with new players entering in the field. It is expected that the next generation of ophthalmologists will have multiple therapeutic options, various drug release kinetics for different diseases as well as new drugs for neurodegeneration, administered preventively using very long-lasting release of low doses of drugs.

Figure legend

Schematic representation of the eye and type of route of administration

ILM: Inner Limiting Membrane, GCL: Ganglion Cell Layer, INL: Inner nuclear layer, ONL: Outer Nuclear layer, ELM: external limiting membrane, RPE: Retinal Pigment Epithelium.

DDS: Drug Delivery System

- [1] J.B. Jonas, R.R.A. Bourne, R.A. White, S.R. Flaxman et al., *Visual impairment and blindness due to macular diseases globally: a systematic review and meta-analysis*, Am. J. Ophthalmol. 158 (2014), pp. 808–815.
- [2] P. Maffi and A. Secchi, *The Burden of Diabetes: Emerging Data*, Dev. Ophthalmol. 60 (2017), pp. 1–5.
- [3] S.J. Bakri, J.E. Thorne, A.C. Ho, J.P. Ehlers et al., *Safety and Efficacy of Anti-Vascular Endothelial Growth Factor Therapies for Neovascular Age-Related Macular Degeneration: A Report by the American Academy of Ophthalmology*, Ophthalmology (2018), .
- [4] Y. Zhu, T. Zhang, G. Xu and L. Peng, *Anti-vascular endothelial growth factor for choroidal neovascularisation in people with pathological myopia*, Cochrane Database Syst. Rev. 12 (2016), pp. CD011160.
- [5] S.D. Solomon, K. Lindsley, S.S. Vedula, M.G. Krzystolik and B.S. Hawkins, *Anti-vascular endothelial growth factor for neovascular age-related macular degeneration*, Cochrane Database Syst. Rev. (2014), pp. CD005139.
- [6] S. Sarwar, E. Clearfield, M.K. Soliman, M.A. Sadiq et al., *Aflibercept for neovascular age-related macular degeneration*, Cochrane Database Syst. Rev. 2 (2016), pp. CD011346.
- [7] S.M. Whitcup, J.A. Cidlowski, K.G. Csaky and J. Ambati, *Pharmacology of Corticosteroids for Diabetic Macular Edema*, Invest. Ophthalmol. Vis. Sci. 59 (2018), pp. 1–12.
- [8] N. Eter, A. Mohr, J. Wachtlin, N. Feltgen et al., *Dexamethasone intravitreal implant in retinal vein occlusion: real-life data from a prospective, multicenter clinical trial*, Graefes Arch. Clin. Exp. Ophthalmol. Albrecht Von Graefes Arch. Klin. Exp. Ophthalmol. 255 (2017), pp. 77–87.
- [9] Y. He, X.-J. Ren, B.-J. Hu, W.-C. Lam et al. , *A meta-analysis of the effect of a dexamethasone intravitreal implant versus intravitreal anti-vascular endothelial growth factor treatment for diabetic macular edema*, BMC Ophthalmol. 18 (2018), pp. 121.
- [10] A. Daruich, A. Matet, A. Moulin, L. Kowalczyk et al., *Mechanisms of macular edema: Beyond the surface*, Prog. Retin. Eye Res. 63 (2018), pp. 20–68.
- [11] J. Talks, V. Daien, R.P. Finger, B. Eldem et al., *Utility of real-world evidence for evaluating anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration*, Surv. Ophthalmol. (2019), .
- [12] E. Boulanger-Scemama, D. Sayag, T. Ha Chau Tran, M. Quaranta-El Maftouhi et al., *[Ranibizumab and exudative age-related macular degeneration: 5-year multicentric functional and anatomical results in real-life practice]*, J. Fr. Ophtalmol. 39 (2016), pp. 668–674.
- [13] A. Malclès, C. Dot, N. Voirin, É. Agard et al., *REAL-LIFE STUDY IN DIABETIC MACULAR EDEMA TREATED WITH DEXAMETHASONE IMPLANT: The Reldex Study*, Retina Phila. Pa 37 (2017), pp. 753–760.
- [14] J. Chhablani, P. Bansal, D. Veritti, S. Sambhana et al., *Dexamethasone implant in diabetic macular edema in real-life situations*, Eye Lond. Engl. 30 (2016), pp. 426–430.
- [15] M. El Sanharawi, L. Kowalczyk, E. Touchard, S. Omri et al *Protein delivery for retinal diseases: from basic considerations to clinical applications*, Prog. Retin. Eye Res. 29 (2010), pp. 443–465.

- [16] M.F. Marmor, *Barriers to fluorescein and protein movement*, Jpn. J. Ophthalmol. 29 (1985), pp. 131–138.
- [17] M.F. Marmor, A. Negi and D.M. Maurice, *Kinetics of macromolecules injected into the subretinal space*, Exp. Eye Res. 40 (1985), pp. 687–696.
- [18] M.F. Marmor, A. Negi and D.M. Maurice, *Kinetics of macromolecules injected into the subretinal space*, Exp. Eye Res. 40 (1985), pp. 687–696.
- [19] K.Y. Janga, A. Tatke, S. Shukla, S.P. Lamichhane et al., *Retina Compatible Interactions and Effective Modulation of Blood Ocular Barrier P-gp Activity by Third-Generation Inhibitors Improve the Ocular Penetration of Loperamide*, J. Pharm. Sci. 107 (2018), pp. 2128–2135.
- [20] H. Chapy, B. Saubaméa, N. Tournier, F. Bourasset et al., *Blood-brain and retinal barriers show dissimilar ABC transporter impacts and concealed effect of P-glycoprotein on a novel verapamil influx carrier*, Br. J. Pharmacol. 173 (2016), pp. 497–510.
- [21] K.-S. Vellonen, L. Hellinen, E. Mannermaa, M. Ruponen et al. *Expression, activity and pharmacokinetic impact of ocular transporters*, Adv. Drug Deliv. Rev. 126 (2018), pp. 3–22.
- [22] E.M. Del Amo and A. Urtti, *Rabbit as an animal model for intravitreal pharmacokinetics: Clinical predictability and quality of the published data*, Exp. Eye Res. 137 (2015), pp. 111–124.
- [23] A.-K. Rimpelä, I. Kiiski, F. Deng, H. Kidron and A. Urtti, *Pharmacokinetic Simulations of Intravitreal Biologicals: Aspects of Drug Delivery to the Posterior and Anterior Segments*, Pharmaceutics 11 (2018), .
- [24] L.A. Hutton-Smith, E.A. Gaffney, H.M. Byrne, A. Caruso, et al *Theoretical Insights into the Retinal Dynamics of Vascular Endothelial Growth Factor in Patients Treated with Ranibizumab, Based on an Ocular Pharmacokinetic/Pharmacodynamic Model*, Mol. Pharm. 15 (2018), pp. 2770–2784.
- [25] E.M. Del Amo, A.-K. Rimpelä, E. Heikkinen, O.K. Kari et al., *Pharmacokinetic aspects of retinal drug delivery*, Prog. Retin. Eye Res. 57 (2017), pp. 134–185.
- [26] J. Yang, X. Wang, G. Fuh, L. Yu et al., *Comparison of binding characteristics and in vitro activities of three inhibitors of vascular endothelial growth factor A*, Mol. Pharm. 11 (2014), pp. 3421–3430.
- [27] P. Lanzetta, A. Loewenstein and Vision Academy Steering Committee, *Fundamental principles of an anti-VEGF treatment regimen: optimal application of intravitreal anti-vascular endothelial growth factor therapy of macular diseases*, Graefes Arch. Clin. Exp. Ophthalmol. Albrecht Von Graefes Arch. Klin. Exp. Ophthalmol. 255 (2017), pp. 1259–1273.
- [28] S. Ming, K. Xie, H. He, Y. Li and B. Lei, *Efficacy and safety of adalimumab in the treatment of non-infectious uveitis: a meta-analysis and systematic review*, Drug Des. Devel. Ther. 12 (2018), pp. 2005–2016.
- [29] P.U. Dugel, G.J. Jaffe, P. Sallstig, J. Warburton et al., *Brolucizumab Versus Aflibercept in Participants with Neovascular Age-Related Macular Degeneration: A Randomized Trial*, Ophthalmology 124 (2017), pp. 1296–1304.
- [30] J.B. Jonas, J.K. Hayler and S. Panda-Jonas, *Intravitreal injection of crystalline cortisone as adjunctive treatment of proliferative vitreoretinopathy*, Br. J. Ophthalmol. 84 (2000), pp. 1064–1067.

- [31] A. Torriglia, F. Valamanesh and F. Behar-Cohen, *On the retinal toxicity of intraocular glucocorticoids*, *Biochem. Pharmacol.* 80 (2010), pp. 1878–1886.
- [32] L.C. Zacharias, T. Lin, R. Migon, C. Ghosn et al., *Assessment of the differences in pharmacokinetics and pharmacodynamics between four distinct formulations of triamcinolone acetonide*, *Retina Phila. Pa* 33 (2013), pp. 522–531.
- [33] R. Bisht, A. Mandal, J.K. Jaiswal and I.D. Rupenthal, *Nanocarrier mediated retinal drug delivery: overcoming ocular barriers to treat posterior eye diseases*, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* 10 (2018), .
- [34] Y. Weng, J. Liu, S. Jin, W. Guo et al *Nanotechnology-based strategies for treatment of ocular disease*, *Acta Pharm. Sin. B* 7 (2017), pp. 281–291.
- [35] Y. Wang, X. Xu, Y. Gu, Y. Cheng and F. Cao, *Recent advance of nanoparticle-based topical drug delivery to the posterior segment of the eye*, *Expert Opin. Drug Deliv.* 15 (2018), pp. 687–701.
- [36] T. Loftsson and E. Stefánsson, *Cyclodextrins and topical drug delivery to the anterior and posterior segments of the eye*, *Int. J. Pharm.* 531 (2017), pp. 413–423.
- [37] A. Ohira, K. Hara, G. Jóhannesson, M. Tanito, et al., *Topical dexamethasone γ -cyclodextrin nanoparticle eye drops increase visual acuity and decrease macular thickness in diabetic macular oedema*, *Acta Ophthalmol. (Copenh.)* 93 (2015), pp. 610–615.
- [38] S.M. Friedman, T.H. Almukhtar, C.W. Baker, A.R. Glassman, et al., *Topical nepafenec in eyes with noncentral diabetic macular edema*, *Retina Phila. Pa* 35 (2015), pp. 944–956.
- [39] O. Weijtens, F.A. van der Sluijs, R.C. Schoemaker, E.G. Lentjes, et al., *Peribulbar corticosteroid injection: vitreal and serum concentrations after dexamethasone disodium phosphate injection*, *Am. J. Ophthalmol.* 123 (1997), pp. 358–363.
- [40] O. Weijtens, R.C. Schoemaker, A.F. Cohen, F.P. Romijn, et al., *Dexamethasone concentration in vitreous and serum after oral administration*, *Am. J. Ophthalmol.* 125 (1998), pp. 673–679.
- [41] O. Weijtens, R.C. Schoemaker, E.G. Lentjes, F.P. Romijn, et al , *Dexamethasone concentration in the subretinal fluid after a subconjunctival injection, a peribulbar injection, or an oral dose*, *Ophthalmology* 107 (2000), pp. 1932–1938.
- [42] M.-H. Errera, M. Westcott, J. Benesty, S. Falah, et al., *A Comparison of the Dexamethasone Implant (Ozurdex®) and Inferior Fornix-based sub-Tenon Triamcinolone Acetonide for Treatment of Inflammatory Ocular Diseases*, *Ocul. Immunol. Inflamm.* (2018), pp. 1–11.
- [43] J.E. Thorne, E.A. Sugar, J.T. Holbrook, A.E. Burke, et al., *Periocular Triamcinolone vs. Intravitreal Triamcinolone vs. Intravitreal Dexamethasone Implant for the Treatment of Uveitic Macular Edema: The PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) Trial*, *Ophthalmology* 126 (2019), pp. 283–295.
- [44] A. Grzybowski, R. Told, S. Sacu, F. Bandello, et al., *2018 Update on Intravitreal Injections: Euretina Expert Consensus Recommendations*, *Ophthalmol. J. Int. Ophtalmol. Int. J. Ophthalmol. Z. Augenheilkd.* 239 (2018), pp. 181–193.
- [45] A. Luaces-Rodríguez, M. González-Barcia, M.J. Blanco-Teijeiro, M. Gil-Martínez, et al., *Review of Intraocular Pharmacokinetics of Anti-Infectives Commonly Used in the Treatment of Infectious Endophthalmitis*, *Pharmaceutics* 10 (2018), .

- [46] M. Edington, J. Connolly and N.V. Chong, *Pharmacokinetics of intravitreal anti-VEGF drugs in vitrectomized versus non-vitrectomized eyes*, *Expert Opin. Drug Metab. Toxicol.* 13 (2017), pp. 1217–1224.
- [47] A. Laude, L.E. Tan, C.G. Wilson, G. Lascaratos, et al., *Intravitreal therapy for neovascular age-related macular degeneration and inter-individual variations in vitreous pharmacokinetics*, *Prog. Retin. Eye Res.* 29 (2010), pp. 466–475.
- [48] M.A. Pen'kov and N.M. Avrushchenko, *[10 years' experience using the suprachoroidal method of administering drugs]*, *Oftalmol. Zh.* 35 (1980), pp. 281–285.
- [49] S. Einmahl, M. Savoldelli, F. D'Hermies, C. Tabatabay, et al. *Evaluation of a novel biomaterial in the suprachoroidal space of the rabbit eye*, *Invest. Ophthalmol. Vis. Sci.* 43 (2002), pp. 1533–1539.
- [50] Z. Habot-Wilner, G. Noronha and C.C. Wykoff, *Suprachoroidally injected pharmacological agents for the treatment of chorio-retinal diseases: a targeted approach*, *Acta Ophthalmol. (Copenh.)* (2019), .
- [51] B. Chiang, J.H. Jung and M.R. Prausnitz, *The suprachoroidal space as a route of administration to the posterior segment of the eye*, *Adv. Drug Deliv. Rev.* 126 (2018), pp. 58–66.
- [52] S. Yeh, S.K. Kurup, R.C. Wang, C.S. Foster, et al., *SUPRACHOROIDAL INJECTION OF TRIAMCINOLONE ACETONIDE, CLS-TA, FOR MACULAR EDEMA DUE TO NONINFECTIOUS UVEITIS: A Randomized, Phase 2 Study (DOGWOOD)*, *Retina Phila. Pa* (2018), .
- [53] A.S. Willoughby, V.S. Vuong, D. Cunefare, S. Farsiu, et al., *Choroidal Changes After Suprachoroidal Injection of Triamcinolone Acetonide in Eyes With Macular Edema Secondary to Retinal Vein Occlusion*, *Am. J. Ophthalmol.* 186 (2018), pp. 144–151.
- [54] A.-K. Rimpelä, I. Kiiski, F. Deng, H. Kidron and A. Urtti, *Pharmacokinetic Simulations of Intravitreal Biologicals: Aspects of Drug Delivery to the Posterior and Anterior Segments*, *Pharmaceutics* 11 (2018), .
- [55] A. Matet, C. Kostic, A.-P. Bemelmans, A. Moulin, et al., *Evaluation of tolerance to lentiviral LV-RPE65 gene therapy vector after subretinal delivery in non-human primates*, *Transl. Res. J. Lab. Clin. Med.* 188 (2017), pp. 40-57.e4.
- [56] Y. Peng, L. Tang and Y. Zhou, *Subretinal Injection: A Review on the Novel Route of Therapeutic Delivery for Vitreoretinal Diseases*, *Ophthalmic Res.* 58 (2017), pp. 217–226.
- [57] D.S. Boyer, Y.H. Yoon, R. Belfort, F. Bandello, et al., *Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema*, *Ophthalmology* 121 (2014), pp. 1904–1914.
- [58] C. Lowder, R. Belfort, S. Lightman, C.S. Foster, et al., *Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis*, *Arch. Ophthalmol. Chic. Ill* 1960 129 (2011), pp. 545–553.
- [59] H. Mehta, M. Gillies and S. Fraser-Bell, *Perspective on the role of Ozurdex (dexamethasone intravitreal implant) in the management of diabetic macular oedema*, *Ther. Adv. Chronic Dis.* 6 (2015), pp. 234–245.
- [60] S. Einmahl, S. Ponsart, R.A. Bejjani, F. D'Hermies, et al., *Ocular biocompatibility of a poly(ortho ester) characterized by autocatalyzed degradation*, *J. Biomed. Mater. Res. A* 67 (2003), pp. 44–53.

- [61] A. Silva-Cunha, S.L. Fialho, M.-C. Naud and F. Behar-Cohen, *Poly-epsilon-caprolactone intravitreal devices: an in vivo study*, Invest. Ophthalmol. Vis. Sci. 50 (2009), pp. 2312–2318.
- [62] G.R. Da Silva, T.H. Lima, R.L. Oréfice, G.M. Fernandes-Cunha, et al., *In vitro and in vivo ocular biocompatibility of electrospun poly(ε-caprolactone) nanofibers*, Eur. J. Pharm. Sci. Off. J. Eur. Fed. Pharm. Sci. 73 (2015), pp. 9–19.
- [63] S.L. Fialho, F. Behar-Cohen and A. Silva-Cunha, *Dexamethasone-loaded poly(epsilon-caprolactone) intravitreal implants: a pilot study*, Eur. J. Pharm. Biopharm. Off. J. Arbeitsgemeinschaft Pharm. Verfahrenstechnik EV 68 (2008), pp. 637–646.
- [64] A. Gupta and B.S. Kim, *Shape Memory Polyurethane Biocomposites Based on Toughened Polycaprolactone Promoted by Nano-Chitosan*, Nanomater. Basel Switz. 9 (2019), .
- [65] D. Lascano, L. Quiles-Carrillo, R. Balart, T. Boronat et al *Toughened Poly(Lactic Acid)-PLA Formulations by Binary Blends with Poly(Butylene Succinate-co-Adipate)-PBSA and Their Shape Memory Behaviour*, Mater. Basel Switz. 12 (2019), .
- [66] C. Andrieu-Soler, R.-A. Bejjani, T. de Bizemont, N. Normand, et al *Ocular gene therapy: a review of nonviral strategies*, Mol. Vis. 12 (2006), pp. 1334–1347.
- [67] A.V. Oliveira, A.M. Rosa da Costa and G.A. Silva, *Non-viral strategies for ocular gene delivery*, Mater. Sci. Eng. C Mater. Biol. Appl. 77 (2017), pp. 1275–1289.
- [68] R. Zulliger, S.M. Conley and M.I. Naash, *Non-viral therapeutic approaches to ocular diseases: An overview and future directions*, J. Control. Release Off. J. Control. Release Soc. 219 (2015), pp. 471–487.
- [69] A.L. Gomes dos Santos, A. Bochot, N. Tsapis, F. Artzner, et al., *Oligonucleotide-polyethylenimine complexes targeting retinal cells: structural analysis and application to anti-TGFβ2 therapy*, Pharm. Res. 23 (2006), pp. 770–781.
- [70] A.L. Gomes dos Santos, A. Bochot, A. Doyle, N. Tsapis, et al., *Sustained release of nanosized complexes of polyethylenimine and anti-TGF-β2 oligonucleotide improves the outcome of glaucoma surgery*, J. Control. Release Off. J. Control. Release Soc. 112 (2006), pp. 369–381.
- [71] J. Yang, *Patisiran for the treatment of hereditary transthyretin-mediated amyloidosis*, Expert Rev. Clin. Pharmacol. 12 (2019), pp. 95–99.
- [72] C.-H. Tsai, P.-Y. Wang, I.-C. Lin, H. Huang, et al, *Ocular Drug Delivery: Role of Degradable Polymeric Nanocarriers for Ophthalmic Application*, Int. J. Mol. Sci. 19 (2018), .
- [73] J.J. Kang-Mieler, E. Dosmar, W. Liu and W.F. Mieler, *Extended ocular drug delivery systems for the anterior and posterior segments: biomaterial options and applications*, Expert Opin. Drug Deliv. 14 (2017), pp. 611–620.
- [74] E.A. Thackaberry, C. Farman, F. Zhong, F. Lorget, et al., *Evaluation of the Toxicity of Intravitreally Injected PLGA Microspheres and Rods in Monkeys and Rabbits: Effects of Depot Size on Inflammatory Response*, Invest. Ophthalmol. Vis. Sci. 58 (2017), pp. 4274–4285.
- [75] G. Soubrane and F. Behar-Cohen, *[Fluocinolone acetonide (ILUVIEN®) micro-implant for chronic diabetic macular edema]*, J. Fr. Ophtalmol. 38 (2015), pp. 159–167.
- [76] J.L. Bourges, C. Bloquel, A. Thomas, F. Froussart, et al., *Intraocular implants for extended drug delivery: therapeutic applications*, Adv. Drug Deliv. Rev. 58 (2006), pp. 1182–1202.

- [77] H. Massa, A.M. Nagar, A. Vergados, P. Dadoukis, et al , *Intravitreal fluocinolone acetonide implant (ILUVIEN®) for diabetic macular oedema: a literature review*, J. Int. Med. Res. 47 (2019), pp. 31–43.
- [78] W. Fusi-Rubiano, R.R. Blow, M. Lane, R. Morjaria and A.K. Denniston, *Iluvien™ (Fluocinolone Acetonide 0.19 mg Intravitreal Implant) in the Treatment of Diabetic Macular Edema: A Review*, Ophthalmol. Ther. 7 (2018), pp. 293–305.
- [79] M.S. Habib, *ILUVIEN® technology in the treatment of center-involving diabetic macular edema: a review of the literature*, Ther. Deliv. 9 (2018), pp. 547–556.
- [80] J.T. Holbrook, E.A. Sugar, A.E. Burke, A.T. Vitale, et al., *Dissociations of the Fluocinolone Acetonide Implant: The Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study*, Am. J. Ophthalmol. 164 (2016), pp. 29–36.
- [81] C.A. Freitas-Neto, A. Maghsoudlou, S. Dhanireddy, A. Payal, et al., *Outcome of Multiple Implants and Dissociation of Fluocinolone Acetonide Intravitreal Implant (Retisert) in a Series of 187 Consecutive Implants*, Ocul. Immunol. Inflamm. 23 (2015), pp. 425–429.
- [82] R.M. Hussain and T.A. Ciulla, *Emerging vascular endothelial growth factor antagonists to treat neovascular age-related macular degeneration*, Expert Opin. Emerg. Drugs 22 (2017), pp. 235–246.
- [83] Y. Liu, S.D. Fortmann, J. Shen, E. Wielechowski, et al., *AAV8-antiVEGFfab Ocular Gene Transfer for Neovascular Age-Related Macular Degeneration*, Mol. Ther. J. Am. Soc. Gene Ther. 26 (2018), pp. 542–549.
- [84] E. Touchard, R. Benard, K. Bigot, J.-D. Laffitte, R. et al., *Non-viral ocular gene therapy, pEYS606, for the treatment of non-infectious uveitis: Preclinical evaluation of the medicinal product*, J. Control. Release Off. J. Control. Release Soc. (2018), .
- [85] S. Russell, J. Bennett, J.A. Wellman, D.C. Chung, et al., *Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial*, Lancet Lond. Engl. 390 (2017), pp. 849–860.
- [86] J.H. Lee, J.-H. Wang, J. Chen, F. Li, et al., *Gene therapy for visual loss: Opportunities and concerns*, Prog. Retin. Eye Res. 68 (2019), pp. 31–53.
- [87] M. Zimmermann, S.J. Lubinga, R. Banken, D. Rind, et al., *Cost Utility of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease*, Value Health J. Int. Soc. Pharmacoeconomics Outcomes Res. 22 (2019), pp. 161–167.
- [88] J.J. Darrow, *Luxturna: FDA documents reveal the value of a costly gene therapy*, Drug Discov. Today (2019), .