Teaser Overview of current and future opportunities for treatment of rare corneal diseases and application of ophthalmic drug delivery systems.

Drug delivery systems and novel formulations to improve treatment of rare corneal disease

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As the field of ocular drug delivery grows so does the potential for novel drug discovery or reformulation in lesser-known diseases of the eye. In particular, rare corneal diseases are an interesting area of research because drug delivery is limited to the outermost tissue of the eye. This review will highlight the opportunities and challenges of drug reformulation and alternative treatment approaches for rare corneal diseases. The barriers to effective drug delivery and proposed solutions in development will be discussed along with an overview of corneal rare disease resources, their current treatments and ophthalmic drug delivery systems that could benefit such cases. The regulatory considerations for effective translation of orphan-designated products will also be discussed.

Introduction

A wide variety of approaches can be employed to address issues of drug delivery in almost every disease and physiological system. This includes reformulation of an existing drug into a form that is safer, more effective or both. Reformulation can include adjustments to the chemical composition of the drug itself or packaging into a carrier to control the rate of drug release [1]. The discovery of new drugs or alternative treatments, such as cell or gene therapy, can also offer hope for improved treatment options for serious conditions. Often, investigational studies for such alternatives are driven by the potential market and the opportunity for disruption of current standards of care.

Ocular disease treatment is of particular interest because of the high incidences of many chronic conditions such as glaucoma and age-related macular degeneration (AMD); and the correspondingly large markets for associated therapeutics. Many first-generation ophthalmic drugs are good candidates for reformulation to improve patient adherence with eyedrop administration, increase tolerability through dose sparing or decrease the cost of ongoing treatment. As

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one example, the effective off-label use of bevacizumab for AMD – and the later FDA approval of its ophthalmic counterparts Lucentis® and Eylea® – has led to a surge of interest in improved retinal drug delivery [2]. Beyond AMD, controlled-release strategies are being employed to develop next-generation glaucoma therapeutics with the goal of bypassing the anatomical barriers to effective ocular drug delivery traditionally associated with eyedrop administration (Fig. 1).

Compared with a widely studied disease affecting the anterior segment like glaucoma, and despite the similarity in location and possible routes of drug administration, far less research has been done in the area of rare ocular diseases. A rare or orphan disease is defined by the FDA as a disease or disorder affecting fewer than 200 000 people in the USA; or affecting more than 200 000 but for which the costs of developing and marketing a therapeutic compound are not expected to be recoverable (adjusted to 2000 individuals in the EU) [3]. The purpose of this review is to highlight the unique opportunities for advancing pharmacologic and other therapeutic approaches for rare diseases of the eye, with particular emphasis on those affecting the cornea. For those diseases that affect the body systemically, the management of systems such as cardiovascular, renal and central nervous system (CNS) are prioritized to extend patient lives. Management of corneal defects, however, can have a tremendous impact on quality of life and should not be neglected.

As the outermost tissue central in the eye responsible for allowing passage of light information to the retina, diseases of the cornea can affect vision in many ways. Fig. 1 shows the anatomical features of the cornea and the associated barriers to drug absorption that will be considered in this review. Among these barriers are the physiological components of the tear film and the cornea. The tear film consists of a lipid layer, aqueous layer and a mucous layer. These components lubricate the corneal surface and aid in maintaining and repairing the corneal epithelium [4]. Although each layer has its own biochemical properties that could interfere with drug delivery, tear turnover rate (1 μl/min) significantly impairs topical drug delivery to ~10–20% bioavailability [5,6]. Further, the cornea itself is a barrier to drug penetration when drug is not lost to convective mechanisms on the ocular surface. Drug diffusion through the cornea is dependent on the layers of the cornea and the physiochemical properties of the therapeutic substance. The cornea is composed of five distinct layers: epithelium, Bowman's layer, stroma, Descemet's membrane and endothelium. Bowman's layer and Descemet's membrane act as transitional, acellular interfaces between the cell layers of the cornea [7] and, as such, do not contribute substantially to permeability rates of drugs through the cornea. The epithelium is the outermost layer of the eye that limits transcorneal diffusion of substances and protects the eye. In particular, the epithelium prevents hydrophilic drugs from absorbing easily owing to its lipoidal properties [8]. The corneal stroma, by contrast, contributes up to 90% of the total cornea thickness and is a diffusional barrier to highly lipophilic drugs. The endothelium does not offer a significant barrier to transcorneal permeability based on hydrophilicity. However, the molecular weight of a given therapeutic agent can be significant, because intracellular junctions can prevent free passage of macromolecules between the stroma and anterior chamber [7].

Despite the significant challenges to topical administration of ophthalmic drugs, this route is generally preferred over systemic

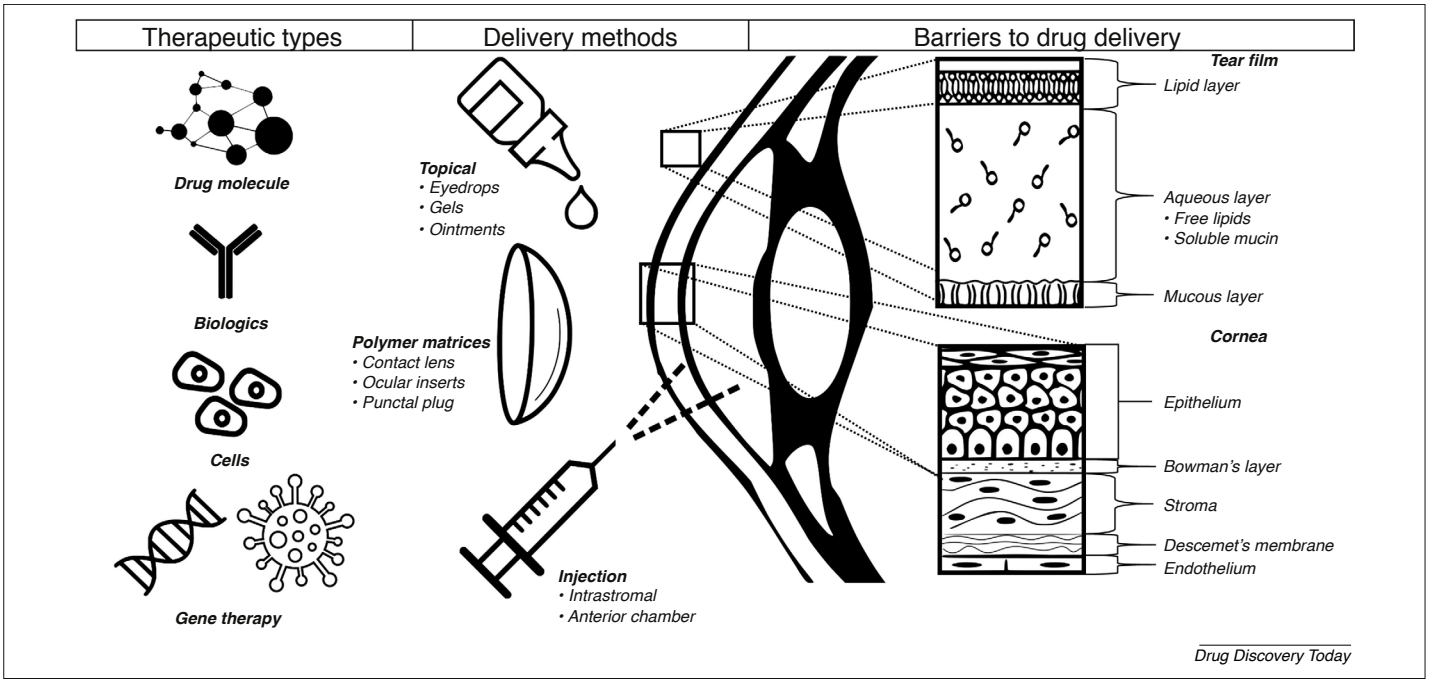

FIGURE 1

Representative categories of corneal drug delivery systems adaptable to a wide variety of therapeutic agents and their associated permeability barriers. Although not inclusive, these delivery methods include topical solutions of soluble therapies, drug loaded ocular inserts (for either cornea, conjunctival or punctal placement) and injections through the cornea. The barriers include tear film and the cornea with various layers that inhibit drug permeation, drug residence time and cellular uptake.

administration. Systemic forms of drug administration, including oral and intravenous routes, are indeed useful in treating many diseases described herein but suffer limitations in treating the ocular manifestations or their symptoms. The anatomical and physiological barriers of the body lead to poor drug distribution to the eye. Orally administered drugs, for example, must pass through the gastrointestinal tract before absorption into the bloodstream [9]. Distribution to various organs and tissues, most notably the liver, severely reduces the amount of drug available to the eye. The relatively small amount of drug that is bioavailable must pass through indirect, selective permeability barriers to reach the cornea because it is an avascular tissue. These include the anteriorly located blood–aqueous barrier and posterior blood–retinal barrier. The blood–aqueous barrier consists of tight junctions in the nonpigmented epithelial layer of the ciliary body and endothelial cells of the iris blood vessels that limit diffusion in the paracellular space [10]. The blood–retinal barrier is located in the retinal pigment epithelial cell layer and uses similar tight junctions to restrict solute permeability from the highly vascular choroid to the subretinal space [11]. For these reasons, the most practical mode of drug delivery is often topical administration.

Many of the challenges associated with topical ocular drug delivery can be overcome with various types of novel drug delivery systems [12]. This includes nanocarriers, suspensions, prodrugs and other novel formulations as well as physical methods such as microneedle arrays and ultrasound-based techniques to disrupt the aforementioned anatomical barriers [7]. Any strategy that prolongs drug residence time on the cornea has the potential to decrease the dosing frequency and improve patient adherence, which for chronic conditions in particular can be low [13]. Increased bioavailability on the ocular surface can also lead to a reduction in the amount of drug required per dose, which can improve the tolerability or toxicity profile of certain medications. Other translational considerations, like protection of the therapeutic payload, storage and shelf-life or cost-effectiveness, can make drug delivery systems an attractive option for reformulating a given compound or investigating new treatments.

It is within the context of the previously described anatomical barriers and the numerous techniques being employed for improved treatment of other ocular diseases that new therapeutic strategies for rare or orphan disorders affecting the cornea (either primarily or secondary to the underlying pathophysiology) will be discussed. Table S1 (see supplementary material online) provides an extensive list of corneal and other diseases to which these strategies might be applicable. Further, the distinct and often advantageous regulatory considerations for translating new drugs and delivery systems for rare diseases will also be discussed.

Categorizing rare diseases of the cornea

There are many resources available to inform clinicians and researchers on rare genetic diseases. The Genetic and Rare Disease Information Center (GARD) as part of the NIH National Center for Advancing Translational Sciences database [14] lists rare diseases and provides supplemental resources for diagnostics, treatment and resources for patient groups and their foundations. Of these resources, the National Organization for Rare Disease (NORD) [15] and Orphanet [16] were used to screen for rare diseases with corneal effects and understand the current available therapies. This widely varied and extensive list (Table S1; see supplementary material online) includes developmental, metabolic, connective tissue, dermatological and other diseases. Many of these diseases also demonstrate multiple ocular manifestations but all share the commonality of affecting the cornea in some way. The Online Mendelian Inheritance in Man (OMIM) number, when applicable, is included to distinguish inherited from non-inherited diseases in this table. Although many of the strategies discussed below have widespread applicability, the genetic basis (or lack thereof) for a given disease must be considered when investigating new treatment options. Our review of these diseases was stratified based on the type of drug available for treating corneal symptoms: no drug (or investigational drugs only), orphan designated drug(s) or non-orphan drug(s). Table 1 provides a summary of the specific diseases discussed in this review.

Rare corneal diseases for which no approved treatment exists

Often, corneal transplantation is the only option when a patient is a candidate and their disease has progressed too far. Although 45 000 (USA) [17] and nearly 185 000 (globally) [18] corneal transplants are performed each year, corneal transplant is often not a permanent solution. An estimated 10% of allografted corneas are rejected after transplantation in avascular, noninflamed host beds (deemed 'low risk' transplantations) [19]. In pediatric corneal transplants, rejection rates are higher and reversibility of graft rejection after treatment is significantly lower than in adults [20]. Immunosuppression therapies can be used to improve outcomes after transplantation, which includes the use of cyclosporin and tacrolimus, and additional long-term studies are ongoing in this area [21]. For example, the use of topical immunosuppression in low- versus high-risk corneal transplantations results in 5-year graft survival rates of 90% and 35% survival rates, respectively [19]. The complexities of allotransplantation combined with ease of access to the cornea makes it a strong candidate for alternative therapeutic options including novel drug discovery [22], gene therapy approaches [23] and cell therapy [24]. Similarly, a recently published review by Moore et al. highlights the potential for genome editing to significantly impact the treatment of corneal dystrophies — a broad and poorly understood category of rare corneal disease discussed in more detail below [25].

One notable disease in this subcategory, mucolipidosis, is a group of lysosomal storage disorders that are characterized by the accumulation of gangliosides, phospholipids and acidic mucopolysaccharides in all tissues [26,27]. Variations in mutations lead to different types and severities of the disease. Of the mucolipidosis diseases, mucolipidosis type IV (ML IV) is strongly associated with severe visual complications [26,28]. Patients with this type of disease experience severe vision loss and blindness by their teenage years. Corneal clouding is bilateral, symmetric and diffuses throughout the cornea [26,29]; and is thought to be caused by accumulation of phospholipids, mucopolysaccharides and gangliosides in the epithelial cells of the cornea [30]. Surgical treatment options for ML IV include conjunctival transplantation, which temporarily resolves opacification through removal of the epithelium [31]. In addition to surgical approaches, several ongoing clinical trials are focused on identifying biomarkers and understanding and documenting the natural history and progression of ML IV patients [32]. Recent studies have also proposed ML IV

TABLE 1

A summary of diseases highlighted in the text with key elements from rare disease resources and relevant orphan drugs

Disease	OMIM no.[a]	Gene	Defective protein	Incidence	Orphan drugs
Mucolipidosis type IV	252650	*MCOLN1*	Mucolipin-1	1 in 40 000; 70% of cases in Ashkenazi Jewish population	N/A
Familial LCAT deficiency Fish-eye disease	245900 136120	*LCAT*	Lecithin-cholesterol acyltransferase	Familial: at least 70 reported cases Fish-eye: at least 30 reported cases	N/A
Galactosialidosis	256540	*CTSA*	Protective protein/cathepsin A	At least 100 reported cases	N/A
Mucopolysaccharidosis type I Scheie syndrome Hurler–Scheie syndrome	607014 607016 607015	*IDUA*	α-l-iduronidase	1.07 in 100 000	Aldurazyme®
Mucopolysaccharidosis type IVA Morquio syndrome IVB	253000 253010	*GALNS*	*N*-acetylgalactosamine-6-s	MPS IVA: 1 in 270 000 MPS IVB:<1 in 1 000 000	Vimzim®
Fabry's disease	301500	*GLA*	α-Galactosidase A	1 in 40 000 to 1 in 117 000	Fabrazyme®
Cystinosis Nephropathic Adult non-nephropathic Late-onset juvenile or adolescent nephropathic cystinosis	219800 219750 219900	*CTNS*	Cystinosin	1 in 100 000 to 200 000	Cystaran™ Cystagon® Procysbi®
Vernal keratoconjunctivitis	N/A	N/A	N/A	3.2 in 10 000 0.8 in 10 000 with corneal complications	Verkazia®

[a] Online Mendelian Inheritance in Man (OMIM) numbers [128] are used to categorize rare disease based on gene and associated defective protein [129]. Incidences are reported from National Institute of Health databases and illustrate rarity [130]. Genetic and Rare Diseases Information Center (GARD) and Orphanet provided orphan drug details [14,16].

models in *Caenorhabditis elegans* and zebrafish that could further elucidate lysosomal defects and cell death [33,34]. These models could provide tools to determine a specific pathway and identify novel drug targets. Treatment of ML IV could benefit from following a similar path to ML II, in which adeno-associated virus serotype 8 (AAV8)-mediated expression of the mutated gene has shown an ability to attenuate deleterious effects of the disease in bones [35].

Indeed, success of other gene therapy models in the cornea would suggest that viral vector incorporation could be straightforwardly tested in appropriate animal models [36]. As one example, corneal fibrosis (a common cause of corneal haziness associated with many of the diseases discussed herein) was treated in an *in vivo* rabbit model and *in vitro* human models using a topical application of combination gene therapy [37]. Corneal fibrosis occurs owing to disorganized extracellular matrix components from myofibroblasts along with decreased expression of corneal crystallin, which are biological processes required for cornea structure and transparency. This particular treatment used gold nanoparticles conjugated to plasmids expressing bone morphogenic protein 7 (BMP7) and hepatocyte growth factor (HGF). The treatment was well tolerated and restored transparency of the cornea *in vivo*. The authors concluded that this effect was mediated by promoting apoptosis in established myofibroblasts via multiple signaling pathways. Although the specific mechanisms underlying injury versus ML-IV-induced corneal haziness are distinct, recent evidence suggests they are associated with the transient receptor potential channel superfamily [38]. Additional research in this area could lead to novel therapies targeting the specific channelopathies in chronic disease.

Familial lecithin cholesterol acyltransferase (LCAT) deficiency is another rare inherited disease affecting the cornea via accumulation of unesterified cholesterol, triglycerides and phospholipids. Corneal opacity occurs as a result of increased lipid deposits in the stroma, which could in turn result in visual impairment [39,40]. Fish-eye disease, partial familial LCAT deficiency, results in severe visual impairment [41,42]. This is a result of diffuse haziness of the corneal stroma, with more-pronounced opacity near the limbus, often arranged in diffuse, grayish, circular bands [43,44]. Severely reduced vision has been treated with corneal transplantation [43]. In addition to treatment with statins and angiotensin receptor blockers [45,46], recent first-in-human clinical studies have investigated novel enzyme replacement therapy with recombinant human LCAT (rhLCAT) [47]. These trials have shown promising results regarding renal function and plasma lipid/LCAT levels and acceptable safety after intravenous (i.v.) infusion [48]. Although it is unlikely that i.v. infusion would affect corneal symptoms, successful translation of rhLCAT therapy could represent a significant step toward development of an ocular formulation.

Galactosialidosis (GS) is a lysosomal storage disease involving cathepsin A – a protein that protects neuraminidase (sialidase) and beta-galactosidase. Deficiency of these two enzymes causes accumulation of sialyloligosaccharides in lysosomes [49,50]. Systemically this can be excreted in body fluids and impacts cardiac function, skeletal growth and neurological disorder. The ocular effects are cherry-red spots of the macula and mild corneal clouding [51,52]. Corneal clouding occurs in early infantile GS, late infantile GS and juvenile and adult forms, with early infantile GS having the most severe corneal effects [53]. These patients die within the first year of life because of suspected kidney and heart failures [52] contributing to a lack of information and research on the management of ocular effects beyond the use of corneal clouding as a diagnostic measure. There are no treatments for GS and treatment is symptomatic and supportive. Animal models of GS involve murine models [54,55] and some preclinical therapies of bone-marrow-mediated *ex vivo* gene therapy [56] and recombinant AAV *in vivo* gene therapy [57]. Like LCAT deficiency, the possibility exists that successful systemic treatment might be

augmented by a cornea-specific treatment or one for the macular spotting primarily responsible for vision loss. Ocular gene therapy has recently become a more viable option because of the late 2017 approval of Luxturna® (Spark Therapeutics) – the first ever direct gene therapy product approved in the USA [58] that targets an inherited form of vision loss caused by retinal dystrophy.

The aforementioned diseases represent a subset of rare diseases associated with corneal pathologies that are potential candidates for investigational therapies to treat those pathologies. Such alternatives could move current treatments from symptom management to actually treating the underlying mechanisms causing dysfunction or damage to the cornea. The process for gaining regulatory approval of new orphan drugs is discussed in a later section, with the end-result being described in the section immediately below.

Rare corneal diseases associated with approved orphan-designated drugs

This category of rare corneal diseases includes examples for which there are approved orphan drug products specifically formulated for ophthalmic use and those for which an ophthalmic version is not (yet) available. When effective drugs are available, reformulation for ophthalmic use is an attractive option. This might include repackaging in a novel drug delivery system, such as sustained- or controlled-release nanocarriers, to avoid or minimize the anatomical barriers to drug absorption mentioned previously.

One such disease with an approved and orphan-designated pharmacologic treatment is mucopolysaccharidosis (MPS), a rare metabolic disease that affects an enzyme involved in the degradation of glycosaminoglycans (GAGs). Accumulation of GAGs occurs in various tissues [59,60], with the degree of enzyme deficiency and type of enzyme giving rise to many subcategories of MPS [61]. The corneal effects of MPS include corneal clouding and accumulation of GAGs in the corneal stroma (Fig. 2). Corneal clouding occurs in all individuals with MPS I, VI and VII and occurs mildly in MPS II and IV; and progression can lead to severe visual impairment (Fig. 2a) [61,62]. Although deep anterior lamellar keratoplasty (DALK) has proven to be a successful surgical method of treating severely cloudy corneas in cases of MPS, not all centers can perform these procedures and a therapy to clear these cloudy corneas without surgery would be extremely beneficial. This is particularly important because outcomes with penetrating keratoplasty tend to be less good than with DALK [63]. There are several therapies currently approved and within investigational clinical trials. In particular, enzyme replacement therapy with alpha-l-iduronidase (IDUA, Aldurazyme®) [64,65] and hematopoietic stem cell transplantation (HSCT) have extended the life of MPS I patients [66,67]. Intrastromal mesenchymal stem cell transplantation has also shown promise in treating corneal clouding in an MPS VII mouse model. In addition to these therapies, preclinical studies for CNS targeting using AAV vectors containing IDUA have been carried out in animal models of MPS I [68,69], including ocular administration topically [70,71] and via intrastromal injection [70]. Topical administration of AAV6, AAV8 and AAV9 were successful in *in vivo* mouse cornea and *ex vivo* donor human cornea [70]. One current limitation is that debridement of the corneal epithelium was performed to achieve high levels of intracorneal transduction. Transduction of AAV8G9 in human corneal stromal cell types resulted in the production of IDUA (>tenfold) after intrastromal injection [72]. Application of AAV in human corneas of MPS I has been demonstrated as well. It was shown that low levels of IDUA efficiently restored wild-type IDUA function in the corneas of MPS I patients [73]. IDUA was overproduced in the human corneal stroma with widespread distribution in multiple cell types, which included cells that naturally produce IDUA [73]. This provides initial validation for ocular gene therapy for MPS I. Further, many controlled-release systems have shown promise for improving the stability and pharmacokinetic profile of biomacromolecules [74,75], which could enable ocular delivery of other forms of treatment for MPS I as well.

Similar to MPS I, enzyme replacement therapy has been offered since 2001 (EU) and 2003 (USA) to treat Fabry disease, a rare metabolic disorder wherein the deficiency of α-galactosidase A leads to depositions of glycosphingolipids in tissues. In ocular structures this accumulation leads to conjunctival vascular abnormalities, corneal opacities (cornea verticillata), lens opacities, cataracts and retinal vascular abnormalities (Fig. 3) [76,77]. Corneal verticillata are whorl-like deposits of lipids in corneal epithelium that are diagnostic for Fabry disease (either female carrier or affected male) but do not impair vision. However, tearing of eyes (lacrimation) and increased corneal sensitivity have been reported in these patients, with artificial tears being prescribed as needed [78,79]. Since the advent of enzyme replacement therapy, the long-term prevention of renal, cardiac and CNS dysfunction

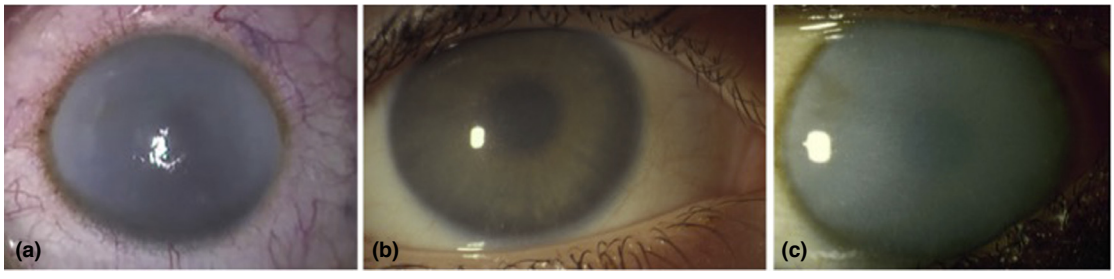

FIGURE 2

Corneal abnormalities in various forms of mucopolysaccharidosis. **(a)** Corneal haze in mucopolysaccharidosis (MPS) I. **(b)** Diffuse corneal haze in Maroteaux–Lamy syndrome (MPS VI). **(c)** Corneal clouding in MPS VII.

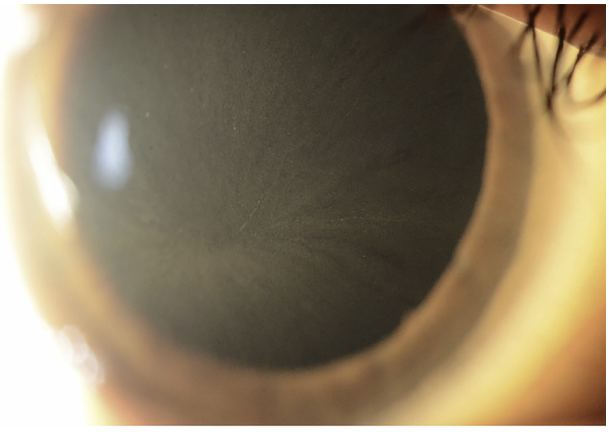

FIGURE 3
Corneal verticillate in Fabry disease.

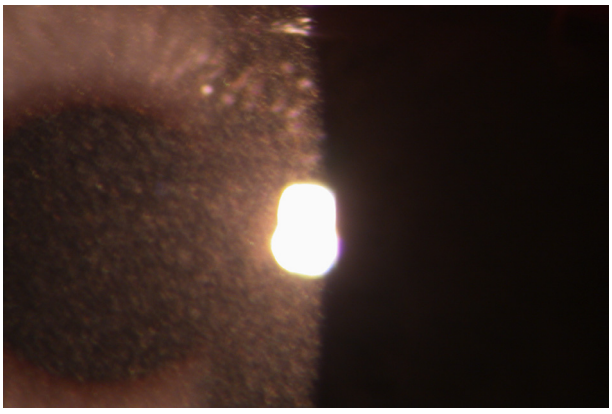

FIGURE 4
Corneal cystine crystal accumulation in cystinosis.

remains to be further established [80]; however, there has been some evidence of reduction of neuropathic pain [81] along with significant improvement in glomerular histology and increase in mean creatinine clearance [82]. Enzyme-replacement-therapy-treated patients exhibiting corneal verticillata, conjunctival vessel tortuosity or cataracts have been studied to investigate the correlation between disease severity and ocular findings [83]. These results suggest that appropriately designed systemic pharmacotherapy can, in some cases, positively impact ocular manifestations. Continued longitudinal analysis of ocular results could further elucidate the benefit to the lacrimal system and retinal vasculature.

Perhaps the best example of orphan drug reformulation is that of cysteamine for the treatment of cystinosis. Cystinosis is a rare autosomal-recessive disease where the protein cystinosin is defective or absent [84,85] resulting in intracellular cystine accumulation in all tissues of the body. The orally administered drug cysteamine (Cystagon®; and its sustained-release counterpart Procysbi®) is effective in removing cystine from many tissues in the body but has no effect on the cornea. Cystine accumulation in the cornea appears as needle-like structures that cause severe light sensitivity, blepharospasm (involuntary closure of eyelids) and significant foreign body sensation (Fig. 4) [85,86]. A clinical trial initiated in 1986 and sponsored by the National Eye Institute tested whether cysteamine eyedrops could remove cystine crystal accumulation from the eyes [87]. The final formulation was approved by the FDA in 2012 as a 0.44% cysteamine ophthalmic solution (Cystaran™). Topical cysteamine has been proven to be safe and effective in dissolving cystine corneal crystals but requires extremely frequent administration — up to once per waking hour — to achieve clinically relevant results [88]. Cysteamine is also highly susceptible to oxidative degradation, therefore requiring that the eyedrops are frozen until opening, stored in the refrigerator and disposed of within 1 week [88]. The high drug concentration and resulting ocular irritation combined with burdensome dosing and storage requirements makes cysteamine a good candidate for reformulation into an encapsulated form that increases bioavailability and drug stability. To this end, recent work has focused on the reformulation of ocular cysteamine into various drug delivery systems. Controlled-release technologies using viscous gels or hydrogels [89,90], prodrugs [91] and loaded contact lenses [92] have been explored using *in vitro* studies. A dissolvable polymer nanowafer has shown reduction of corneal cystine crystals in a rodent model of cystinosis [93]. Recent efforts in translating clinical trial study results into EU orphan drug approval have been successful with the introduction of Cystadrops® in 2017–carmellose sodium gel formulation with cysteamine [94,95]. The recommended dosing for Cystadrops® is four-times daily, representing a significant reduction in administration frequency over Cystaran™ (up to 12-times daily); however, patients still report pain upon instillation and an increase in mean intraocular pressure after 12 months [94]. The local side-effect of pain is inherent to similar cysteamine concentrations, suggesting patients favor a viscous gel formulation over traditional cysteamine eyedrops if local pain is still exhibited. Beyond pharmacologic approaches, current clinical studies seek to address the genetic mutation underlying cystine accumulation in cystinosis as an alternative to lifelong cysteamine administration. Hematopoietic stem and progenitor cell transplantation have been explored in rodent models to establish the therapeutic effect of transport of cystinosin to diseased cells, which have shown clearance of corneal cystine crystals [96]. Interestingly, these studies did in fact demonstrate stem cell localization in the cornea and rescue of ocular defects, including a reduction in corneal cystine crystals and restoration of normal corneal thickness [96]. The need, if any, for supplementary therapy with cysteamine eyedrops to support stem cell transplantation will not be fully understood until future evaluation of clinical results. To this end, the first report of human hematopoietic stem cell transplantation was published in July 2018 [97].

Rare corneal diseases treated with non-orphan-designated drugs

Often the ocular symptoms associated with rare diseases, particularly intracellular diseases affecting multiple systems or tissues, are managed using supportive pharmacotherapy with common, FDA-approved drugs. These drugs, including anti-inflammatory and immunosuppressive agents, have broad applicab ility as ophthalmic therapeutics. Still, they are subject to all of the aforemen-

tioned barriers to effective intraocular absorption in and around the cornea. Significant work has been done in the area of reformulating these classes of drugs into controlled- or sustained-release formulations. Thus, the investigation of novel drug delivery systems for these more common pharmaceutical agents is one that might offer substantial benefit to patients with diseases in this subcategory.

One example of approved, reformulated steroids is the Ozurdex® implant, used to treat macular edema and noninfectious uveitis [98]. This rod-shaped intravitreal implant is administered every 6 months at a maximum, during which time it slowly degrades and releases dexamethasone. Although not specifically used in a topical administration, this example is noteworthy because similar degradable materials can be used for ocular surface or anterior chamber indications. Indeed, investigational techniques have attempted to locally and sustainably deliver corticosteroids for such purposes as managing post-cataract surgery inflammation, inflammatory eye diseases or injury. This includes a depot placed in the canaliculus [99], polymeric nanoparticles [100], drug-loaded contact lenses [101,102] and nanowafers similar to those used for cysteamine delivery [103], among many others.

The treatment of vernal keratoconjunctivitis (VKC) highlights many of the topics discussed in this review — with non-orphan drug use and a recently approved orphan drug product to manage the variety of symptoms associated with the disease. VKC is a chronic allergic condition that affects the ocular surface, thought to be IgE and T-cell-mediated and typically leading to chronic inflammation [104,105]. The disease is characterized by papillary conjunctivitis in the upper eyelids, which can progress to giant papillae and development of gelatinous nodules in the limbus area of the cornea. Papillary conjunctivitis is the irritation of the thin, translucent lining of the eye and the undersurface of the eyelids. It is often caused by bacteria, viruses and, in this case, allergies. Although VKC is often self-limiting, severe cases can lead to corneal shield ulcers and cataracts. Additionally, patients experience light sensitivity, blepharospasm, redness and thick mucus discharge [106–108]. Treatment is generally focused on relieving specific symptoms. This includes the use of mast cell stabilizers (such as sodium cromoglicate, nedocrimil, lodoxamide, pemirolast) and antihistamines (such as levocabastine and emedastine). Severe forms of VKC can be treated using nonsteroidal anti-inflammatory eyedrops including indomethacins 1%, ketorolac 0.5% and diclofenac 0.1% [109–111]. In addition, immunosuppressive agents such as topical cyclosporine and tacrolimus have been used as an alternative treatment when corticosteroid-induced ocular hypertension or other side-effects are of particular concern [112–114]. Recently, a cationic nanoemulsion of cyclosporine (Verkazia®) was approved by the European Commission (EC) and European Medicinal Agency (EMA) and granted orphan drug designation in 2018 with the intended purpose of increasing residence time on the ocular surface through electrostatic attraction with a negatively charged mucosal layer [115].

Corneal dystrophies

At the intersection of genetic corneal diseases and poorly understood, rare conditions, we find a group of progressive eye disorders called corneal dystrophies (Table S1; see supplementary material online). The high number of corneal dystrophies and wide range of treatment options make this a unique category in a review of rare corneal diseases. The severity of visual effects resulting from corneal dystrophies ranges from asymptomatic to significant vision impairment (Fig. 5). In many patients, the cornea can become cloudy with accumulation of material leading to photophobia, recurrent corneal erosion and foreign body sensation [116,117]. Corneal dystrophies are often bilateral, symmetric and not related to environmental or systemic factors. In the past decade, there have been large efforts by clinicians and researchers to categorize types of corneal dystrophies. The International Committee for Classification of Corneal Dystrophies (IC3D) has been responsible for defining each one based on genetics, corneal layers and clinical outcomes [117]. The IC3D has expressed many challenges in distinguishing types and approaches to treat each type; there is currently no standard treatment for corneal dystrophies owing to the vast differences among them. Some similarities in possible treatment can be found by categorizing according to which layers of the cornea are affected. If the endothelium (the innermost layer adjacent to aqueous humor) is affected an endothelial keratoplasty or transplant might be considered. Anterior stromal dystrophies, by contrast, can be treated by superficial keratectomy. Dystrophies of the epithelium can be treated conservatively with bandage contact lenses, lubricating eye drops or even alcohol delamination – an approved treatment for corneal epithelium removal for recurrent corneal erosions [117].

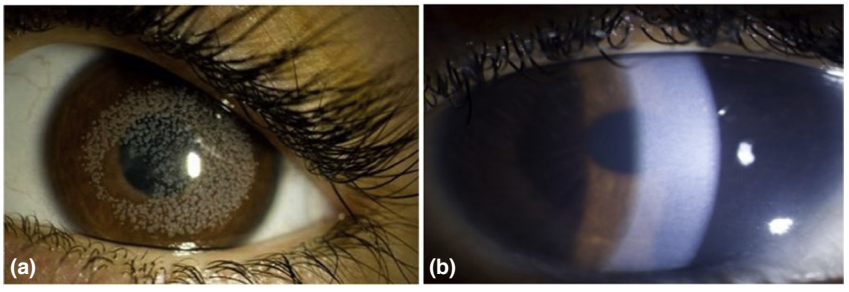

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FIGURE 5

Corneal abnormalities in two types of corneal dystrophies, illustrating the vast differences within this broad category of rare corneal disease. **(a)** Anterior stromal deposits characteristic of combined granular-lattice corneal dystrophy. **(b)** Corneal edema and clouding in congenital hereditary endothelial dystrophy (CHED).

Limbal stem cell deficiency (LSCD), although not categorized as a corneal dystrophy, has been granted orphan designation and is currently being treated with a recently approved product called Holoclar®. Holoclar® was the first stem-cell-based medicinal product approved in the West. It uses a disc made of limbal stem cells expanded in culture after taking a biopsy from a small section of healthy limbus [118]. This is particularly useful in cases where bilateral LSCD is present (precluding autologous transplant), as is common in several corneal dystrophies in which damage to the limbus occurs. Another complication of LSCD and other forms of trauma to the cornea is persistent corneal epithelial defect, for which EyeVance Pharmaceuticals' Nexagon® has recently received orphan designation. This treatment modality, an antisense oligonucleotide that downregulates expression of the gap junction protein Connexin 43, has shown promising results in wound healing for burns and trauma [119,120] and will soon begin its clinical evaluation. Further studies will elucidate the role of treatments like Holoclar® and Nexagon® in improving outcomes for the widespread forms of corneal dystrophies, specifically those associated with epithelial dysfunction [121]. Beyond these specific methods, and similar to the other rare corneal diseases highlighted herein, reformulation techniques to improve key properties like stability, biocompatibility and efficacy of conventional treatments have the potential to significantly enhance the quality of life for patients with corneal dystrophies.

Translational considerations for orphan drug and disease research

A 2016 study estimated the pre-tax, preapproval costs of developing new drugs and biologics at US$2.6 billion; and the time to approval lasting a decade or more [122]. This is specific to products following the FDA's new drug application (NDA) or biologic license application (BLA) pathway and includes the cost and time associated with failed compounds. Thus, the resources required for developing new therapies for any disease can be a significant barrier to progress.

Several factors relevant to the topics discussed in this review can influence the preapproval cost and time expenditure. This includes the Orphan Drug Tax Credit, established after passage of the Orphan Drug Act of 1983, to offer financial encouragement for R&D in smaller markets. Specifically, 50% of the qualified costs of clinical research and testing can be claimed for this credit. In 2015, one study estimated that 33% (67 fewer) of the orphan products approved in the period 1985–2015 would not have been developed without these tax credits [123]. The FDA's Office of Orphan Products Development (OOPD) has reported that, in contrast to only ten products approved for orphan indications between 1973 and 1983, >600 have been developed and marketed in the time since 1983. Costs are further reduced by the smaller number of patients typically required for clinical testing of orphan products. Further, the first sponsor of a designated orphan product to receive FDA marketing approval for a given rare condition is granted 7 years of market exclusivity in the USA (10 years in the EU). This can extend the protection of the associated intellectual property in the common circumstances where the patent expires before or soon after marketing approval.

In the case of rare pediatric diseases, an even more specialized designation, additional incentives have been established. The definition of rare pediatric disease was clarified in the Advancing Hope Act of 2016 to be a serious or life-threatening disease, in which the most severe manifestations affect individuals from birth to 18 years old, that also meets the criterion for rare disease designation [124]. A 2014 draft guidance document issued by the FDA specified that, under section 529 of the Federal Food, Drug and Cosmetic Act, a sponsor for an approved orphan product for a rare pediatric disease could receive a priority review voucher (PRV) for the expedited review of a subsequent product [125]. Interestingly, the PRV is transferable and can be used for review of non-orphan products, providing significant incentive to the original sponsor and organizations wishing to purchase the PRV. Such was the case for the Spark Therapeutics after development of Luxturna®; in 2018 their PRV was sold for US$110 million. The demand for PRVs has dropped significantly since peaking in 2015, however, possibly owing to the increased number available through additional PRV programs for counterterrorism and tropical diseases [126].

Despite modern advances in motivating sponsors to pursue orphan indications, the number of patients with the disease can heavily influence the out-of-pocket cost of the approved drug to those patients. This is particularly true in cases where the orphan product is not being sought for any other indications, as with the >US$200 000 yearly cost of Aldurazyme® for the ultra-rare disease MPS I, considered to be one of the most expensive drugs marketed today. The financial and ethical ramifications for marketing of orphan products has been the subject of much debate, most recently surrounding patient access to cysteamine bitartrate for cystinosis [127]. This case study is especially poignant given that a private non-profit foundation supported primarily by cystinosis patients and their families funded the preclinical development of enteric-coated cysteamine. That same delayed release formulation, now marketed under the name Procysbi®, raised the yearly cost from ~US$8000 at the time of its approval in 2013 to >US$250 000 despite following the 505b(2) pathway rather than development as a new chemical entity. A 505b(2) NDA allows a portion of the safety and efficacy data to come from studies conducted on the previously approved drug, even when those studies were not done by or for the new sponsor, resulting in a less costly and time consuming path to approval. Despite this benefit to sponsors, insurance reimbursement can be problematic for reformulated drugs that cost more than their generic counterparts when the main differences are those of convenience or tolerability over efficacy or safety. The question of pricing versus value offered to patients and their families is unique to each drug and disease and well beyond the scope of this review, but a necessary consideration for engaging in rare and ultra-rare disease research.

Concluding remarks

As the field of ocular drug delivery continues to make progress in translating innovative, next-generation therapeutics for highly prevalent eye diseases, there remains substantial potential for similar approaches to improving treatment of rare conditions. Many of the corneal manifestations of these diseases can be treated with common medications that are already being reformulated into sustained- or controlled-release systems. Other rare or ultra-rare conditions would benefit from additional research into novel

pharmacologic, cell or gene-based approaches to address the underlying pathologies. The FDA recognizes the benefit that can potentially be conferred to patients and the research community by incentivizing such discoveries. As such, research at the interface of vision and rare disease research has already led to the development of successful new or reformulated products and will probably continue to do so in the future.

With the advantages offered by orphan drug legislation, the treatment of rare corneal diseases as with all rare diseases should be better addressed now than ever before. As with any disease, however, finding a compatible match for drug, disease and delivery system is of key importance to advance treatments to the clinic. Perhaps the greatest hope for achieving this goal lies in understanding the unique scientific questions inherent to corneal disease: specifically, what combination of safely addressing vision complications and comfort will lead to the greatest positive impact on patient quality of life? As basic science researchers continue to elucidate genetic influences and define new targets and pathways for rare corneal diseases, there remains a significant opportunity in reformulation of existing drugs for the drug delivery research community.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drudis.2019.03.005.

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