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The Evolving Landscape of Dry Eye Disease Therapies

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Abstract

Dry eye disease (DED) is a prevalent disorder of the ocular surface and tear film for which currently no fully satisfactory treatment exists, reflecting its multifactorial nature and perhaps inherent limitations of existing treatments. Responding to this unmet medical need, the research community and pharmaceutical industry display robust activity in the development of novel approaches to DED treatment. These efforts include pharmaceutical agents and devices directed at various pathogenetic aspects of this still incompletely understood disease. Here, we review current and under development treatments and assess the state of this evolving field.

Keywords: Dry Eye Disease; Cyclosporin; Lifitegrast; Diquafosol; Rebamipide; Varenicline; Phosphosulindac

Abbreviations: CAM: Cryopreserved Amniotic Membrane; DED: Dry Eye Disease; NGF: Nerve Growth Factor; PS: Phosphosulindac

Introduction

Dry eye disease (DED) is a multifactorial disorder of the ocular surface and tear film, with high worldwide prevalence and a significant impact to patient's quality of life. It is characterised by disruption of the homeostasis of the tear film, leading to tear film instability and hyperosmolarity along with ocular surface inflammation [1]. Subsequent inflammation of the eyelid margin and changes to the ocular nervous system further complicate DED. DED is divided into 3 subtypes: aqueous-deficient, evaporative and mixed [2]. DED can present with any combination of several symptoms such as dryness, grittiness, itching and burning sensations [3]. Ocular pain has also been reported, the cause of which is not only nociceptive, but can also be neuropathic and psychogenic [4]. While symptoms of DED have been found to correlate with increased corneal sensitivity, signs of DED have been found to correlate poorly. This indicates that the quality of tear film and tear homeostasis are not the only factors influencing DED, with the corneal somatosensory system likely affecting patient symptoms and causing neuropathic pain [5]. DED has detrimental effects on physical and mental quality of life, with significant economic burden to healthcare [6]. The annual direct cost per DED patient in the USA has been estimated to be $783, with the total annual cost of DED to the United States healthcare estimated at $3.84 billion [7]. The number of treatments available for DED has been progressively increasing. Given the multifactorial and often treatment-resistant nature of DED, there is large variation in existing treatments in terms of mode of action and application. This mini-review aims to describe the current landscape of DED therapies and highlight therapies under development.

Current Drug Therapies

The current mainstay and first-line treatment of DED is through topical drug therapy in the form of eye drops or emulsions. Artificial tears are the most used DED treatment. They help protect and lubricate mucous membranes while diluting pro-inflammatory factors in tears and making the ocular surface less susceptible to inflammation. While they help prevent the buildup of symptoms, they do not treat the causes of DED [8]. Anti-inflammatory agents are often employed in DED treatment to help control the inflammatory aspect of the disease. Cyclosporine has anti-inflammatory and immunosuppressive properties, leading to varied improvement in DED signs and symptoms, although causing significant eye irritation on application [9]. Topical

corticosteroids are also being used as a short-term therapy; however, their long-term use can lead to high intraocular pressure and cataract formation. Fatty acid omega-3 and -6 supplements have been shown to exhibit anti-inflammatory effects resulting in an improvement in DED symptoms [2].

As part of treating eyelid inflammation, which is often present in DED, antibiotics have been employed. Short-term use of oral tetracyclines or topical azithromycin can reduce the activity of inflammatory agents and help treat meibomian gland dysfunction, which can otherwise perpetuate DED [10]. Lifitegrast, a T-cell integrin antagonist, improves several clinically relevant parameters of DED, with rather infrequent mild to moderate side effects. Dysgeusia, instillation site pain, and irritation may be a concern for some. Overall, most of the adverse events are tolerable and lifitegrast can alleviate refractory DED and improves patients' quality of life [11]. The recently introduced varenicline, a nicotinic acetylcholine receptor agonist, is innovative in its route of administration [12]. Given as a nasal spray, varenicline acts rapidly and is effective and generally well tolerated, with its increase in endogenous tear secretion being a potentially useful advantage over existing therapies. More follow-up studies are needed for its full assessment.

New Treatments

A number of new topical therapies currently in clinical trials are mucin-like glycoproteins and mucin secretagogues. Mucins are normally secreted by goblet cells and are responsible for stabilizing the tear film and providing lubrication. Their absence also increases shear stress and results in the release of inflammatory factors. Diquafosol and rebamipide are two mucin secretagogues that have been approved for use in Japan which have achieved increased mucin production through an increase in goblet cell numbers, leading to improvement in DED signs and symptoms [2,13]. A novel anti-inflammatory drug, phosphosulindac (PS), has demonstrated promising preclinical results. Topical treatment with PS in rabbits with induced DED was more efficacious compared to cyclosporine and lifitegrast, the currently most used anti-inflammatories [14]. In another preclinical study, all 3 DED subtypes were simulated in rabbits and PS was able to rapidly reverse almost all measured DED parameters in each subtype. Most impressively, PS normalised corneal sensitivity with once-daily dosing and without side-effects [15]. The use of cryopreserved amniotic membranes (CAM) has been evaluated in the treatment of DED. CAM is already being used for its anti-inflammatory properties in other conditions, and it was demonstrated that it aids in the restoration of corneal nerves in DED, likely due to its high nerve growth factor concentration [16].

New devices are being developed to help treat DED, particularly helpful in patients with aqueous-deficient DED. Neurostimulation devices have been introduced for the treatment of DED that work by stimulating tear production by applying electrical currents a few times a day. However, these devices are costly and uncomfortable to use [17]. Biosensor integrated contact lenses are also being developed, aimed at analysing tear film biomarkers and using that information to help guide DED therapy [18]. Novel methods of drug delivery are also being introduced to increase drug bioavailability while improving ease of use. Current eye drops or emulsions are rapidly eliminated from their site of application, resulting in low bioavailability and requiring frequent dosing [18]. Novel particulate systems for topical administration have been developed, termed nanoparticles, which help improve drug absorption with prolonged drug release [19]. Contact lenses are being developed as ocular delivery systems, aiming to provide sustained release of medication. However, they carry inherent risks of corneal damage and infection, while different contact lens models have had issues with initial burst release of the drug or leeching of medication during storage [20,21].

Discussion

DED is a chronic and treatment resistant condition without an available definitive treatment. An optimal treatment would be able to treat the multifactorial nature of DED with infrequent dosing and minimal side-effects. Current treatment regimens require multiple application of drops daily and often do not target all aspects of DED. Rather than treating DED with a single stepwise escalation of drug therapy and interventions, evaluation of each individual is required to determine which of the multifactorial causes of DED are present. A targeted approach, which considers the 3 pathogenic pillars of DED (tear film instability, inflammation, and epithelial damage with loss of function), can help identify the most important causative factor and help tailor treatment. A treatment regimen that combines different degrees of inflammation management, epithelial protection and lid management can help achieve a patient-tailored comprehensive DED treatment [22]. An important DED aspect that is not addressed with current treatments is its neurogenic components. Phosphosulindac animal trials demonstrated normalisation of corneal sensitivity while also being anti-inflammatory and improving tear film stability, while achieving once-a-day dosing without side-effects [15]. Research is also ongoing for neurogenic focused treatments, including human recombinant nerve growth factor, which is currently used to treat neurotrophic keratitis [8].

For any treatment to be successful, it requires the appropriate compliance from the patient. Current DED treatment regimens require frequent dosing throughout the day, with the most common method of drug delivery being eye drops. Studies looking at glaucoma treatment, which also depends on multiple applications of drops per day, demonstrate difficulty for patients to remain adherent. Simplifying medication regimens and reducing the applications required in a day would likely improve compliance [23]. And the use of drops as a drug delivery system

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creates a challenge for patients, as they have difficulty instilling drops correctly [24]. Thus, an optimal DED treatment should be simple to carry out and apply, while requiring the least number of dug applications.

Conclusion

DED is a common multifactorial disease for which we still do not have an optimal treatment. DED treatment should be selected on an individual basis and tailored to disease progression. There are currently many novel DED therapies in development, which promise to be more effective, safer, and easier to use compared to currently available treatments. An optimum treatment regimen should target all aspects of DED, while allowing infrequent and simple dosing.

Conflicts of Interest

The authors report no conflict of interest except for BR who has equity positions in Apis Therapeutics LLC and Medicon Pharmaceuticals. Inc.

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