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Emerging targets of inflammation and tear secretion in dry eye disease

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The underlying mechanisms of dry eye are thought to be part of a vicious circle involving a hyperosmolarity-triggered inflammatory cascade, resulting in loss of goblet cells and glycocalyx mucin and observed corneal and conjunctival epithelial cell damage. This damage leads to increased tear film instability, further hyperosmolarity and hence perpetuating of a vicious circle. The aim of dry eye management is to restore the homeostasis of the tear film and break the perpetuation of this vicious circle. Despite the plethora of treatment options available, many of these are largely palliative, short-lived and require repeated instillations. Two emerging areas in dry eye therapy aim to promote tear secretion and to safely manage dry eye-associated inflammation and are the focus of this review.

Dry eye disease and its treatment

Dry eye disease is defined by the Tear Film and Ocular Surface Dry Eye Workshop (TFOS DEWS) II as ``a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" [1]. The underlying mechanisms of dry eye are thought to be part of a vicious circle involving a hyperosmolarity-triggered inflammatory cascade, resulting in loss of goblet cells and glycocalyx mucin and observed corneal and conjunctival epithelial cell damage [2]. This damage to the ocular surface leads to increased tear film instability, further feeding tear hyperosmolarity and hence perpetuating the vicious circle [2] (Fig. 1). Traditionally, the disease has been characterized into aqueous deficiency and evaporative dry eye, but it is now understood that both conditions lie on a continuum that can be present simultaneously to a varying degree [1].

The aim of dry eye management is to restore the homeostasis of the tear film and break the perpetuation of the dry eye circle [3]. Current treatments can be largely categorized into one of six categories: treatment for aqueous deficiency, treatment for meibomian gland dysfunction and eyelid abnormalities, anti-inflammatory therapy, surgical approaches, dietary modifications and environmental modifications [3]. Despite the plethora of treatment options available, many of these are largely palliative, short-lived and require repeated instillations [4]. Two emerging areas in dry eye therapy aim to promote tear secretion and to safely manage dry eye-associated inflammation (Fig. 1) and are the focus of this review.

Promoting tear secretion

Topical pharmaceutical secretagogues

Secretagogues stimulate the secretion of the aqueous, mucin or lipid constituents of the tear film, hence minimising the impact of tear film instability and goblet cell and glycocalyx mucin loss that form part of the vicious circle of dry eye disease [2]. The following discussion separates secretagogues into those that stimulate each of these constituents, however it should be recognized the potential for overlapping effects affecting multiple components of the tear film.

Aqueous secretagogues

Diquafosol tetrasodium (3% ophthalmic solution, Diquas®; Santen, Osaka, Japan) is approved for use in Japan and South Korea. This is a mucolytic compound and a purinergic $P2Y_2$ receptor agonist that stimulates tear fluid and mucin secretion [5,6]. P2Y receptors are meta-

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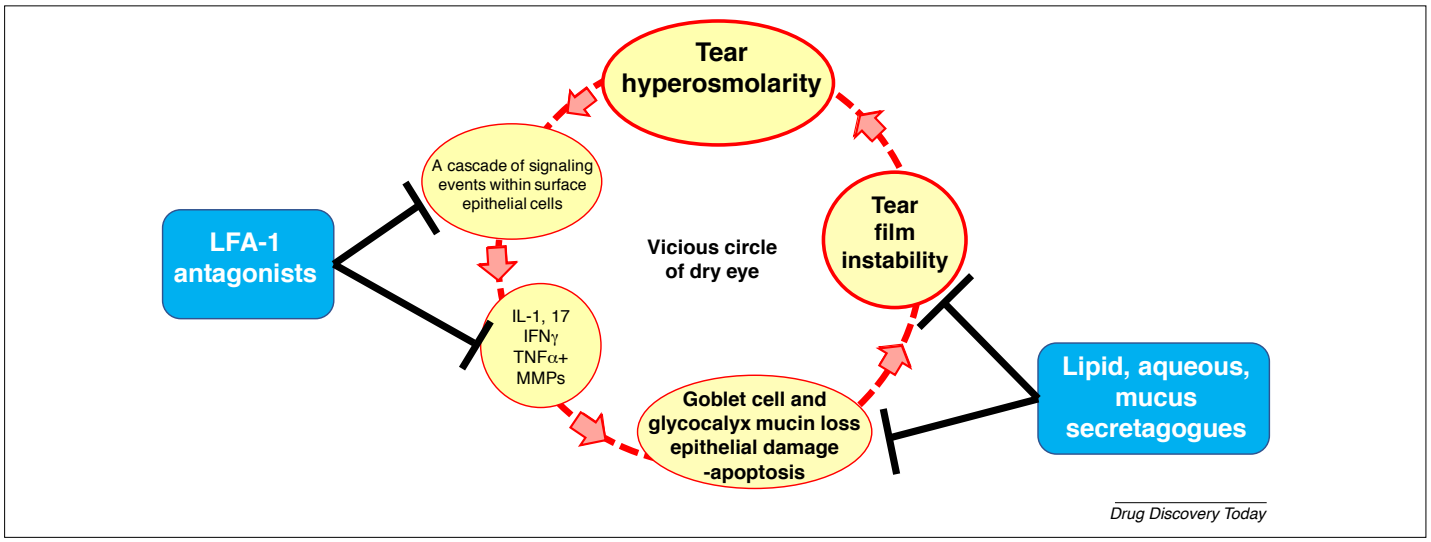

FIGURE 1

The vicious circle of dry eye disease (adapted from Bron, A.J. et al. (2017) TFOS DEWS II pathophysiology report. Ocul Surf 15 (3), 438–510) [1]. The core mechanisms of dry eye disease are thought to be tear hyperosmolarity which leads to a cascade of signalling events within epithelial cells. This leads to inflammation which further leads to ocular surface damage and tear film instability. Without intervention, this circle is thought to be self-perpetuating. The proposed actions of the two emerging treatments for dry eye disease presented in this review, secretagogues and lymphocyte function-associated antigen-1 antagonists (LFA-1 antagonists) on this cycle are shown in the blue. IL: interleukin, IFNϒ: interferon gamma, TNFα: tumor necrosis factor alpha, MMPs: matrix metalloproteinases.

botropic guanosine triphosphate binding protein (G-protein) coupled receptors and $P2Y_2$ receptors specifically activate phospholipase C-β [7]. These receptors are found at the corneal epithelium, the conjunctival epithelium, the goblet cells and meibomian glands [8]. In age-related dry eye mice models, use of diquafosol results in increased goblet cell density and a decrease in ocular surface inflammation [9]. Byun *et al.* demonstrated that diquafosol accelerates corneal epithelial wound healing possibly as a result of epidermal growth factor receptor/extracellular signal-regulated kinase stimulated cell proliferation and migration [10]. Other studies have shown effects of the drug to suppress the loss of corneal epithelial integrity [6,11].

Several randomized controlled clinical trials have demonstrated the efficacy and safety of diquafosol administered topically for dry eye disease [12–14]. In a 4-week randomised, double-masked study of 286 patients with dry eye disease comparing diquafosol 3% to sodium hyaluronate ophthalmic solution, each taken 6 times daily for 4 weeks, diquafosol significantly improved conjunctival staining scores while having a similar adverse event profile as the sodium hyaluronate [15]. Combining these two products has been shown to be effective in stabilizing vision and dry eye symptoms following LASIK [16]. In a randomized, parallel-group comparison study of 497 patients with dry eye disease over a 4-week period, diquafosol resulted in an improved fluorescein staining score similar to the control group that was taking 0.1% sodium hyaluronate ophthalmic solution, and even further improvements in rose bengal staining, more so than the control [12]. In a prospective study evaluating 3% diquafosol sodium on 13 patients over a 3-month period, an improvement in meibomian gland appearance and function and symptoms was found [17]. In a study of 15 patients with aqueous deficient dry eye disease treated for 6 months, an improvement in symptoms, corneal staining, tear break-up time and tear meniscus height was noted after 1 month and maintained for the 6-month observation period [18]. Other studies have supported similar findings for diquafosol's impact on the ocular surface, showing an improvement in symptoms and corneal staining [19], tear volume [20,21], lid margin abnormalities including vascularity [22], corneal staining [23,22], meibomian gland function [22] and lipid layer thickness [24]. Diquafosol's ability to improve higher order aberrations has been reported, but other studies have contradicted this, suggesting its impact on this parameter to be equivocal [25–29]. There have also been little to no studies on the long-term usage of this agent and it currently remains unavailable to most areas within the world.

Lacritin is a tear glycoprotein prosecretory mitogen that promotes basal tear secretion [30] and epithelial homeostasis [31]. It is downregulated in both Sjögren's Syndrome [32] and contact lens-related dry eye disease [33]. In the presence of ocular surface inflammation, lacritin is down-regulated by tear tissue transglutaminase which is elevated in dry eye disease [34,35]. Lacritin's application in dry eye disease is aimed at taking advantage of tear proteins as potential biotherapeutics. In mice models of Sjögren's Syndrome treated with lacritin, treatment with lacritin demonstrated a 46% increase in tear secretion and a reduction in lissamine green staining, compared to the control eyes [32]. On the cornea it also resulted in a shift from skin-specific cytokeratin to K12, a corneal-specific cytokeratin that is abundant in the healthy ocular mucosal epithelium [32]. The drug is currently not available commercially although it is being evaluated for its safety and efficacy in an ongoing human clinical trial (NCT03226444), with an estimated 201 participants randomised to receive either 0.005% or 0.01% Lacripep™, or placebo [36].

Mucin secretagogues

Rebamipide ophthalmic suspension (Mucosta®; Otsuka Pharmaceutical, Chiyoda, Japan) is a mucin secretagogue that promotes the production of mucin-like glycoproteins in human corneal epithelial cells [37] as well as the expression of membrane-associated mucins MUC1, MUC4 and MUC16 [37]. Currently in Japan, along with hyaluronic acid and diquafosol, it forms the mainstay of dry eye treatment [38]. Rebamipide was originally launched as an

oral medication for the repair of gastric mucosa [39]. Topically, it has been shown to increase the mucin secreted by conjunctival goblet cells [40], and to improve conjunctival epithelial differentiation and suppress keratinization [41], and to therefore have utility as a form of dry eye therapy [42]. In the murine models of both dry eye disease and Sjögren's Syndrome it has been shown to have an anti-inflammatory effect [43,44] and to be protective of the ocular surface when administered topically [45] by protecting the epithelium from TNF-a induced disruption of barrier function [46]. In rabbits, when applied 6 times a day for 14 days it has been shown to increase mucin-like substances in the cornea and conjunctiva and to decrease conjunctival staining [47]. In corneal epithelial cells rebamipide significantly increases the glycoconjugate contents in the cells, an effect that is mediated by MUC1 and MUC4 gene expression [48].

Clinical trials of rebamipide have been conducted over the course of four weeks. A 2% topical rebamipide drop instilled 4 times a day for 4 weeks has been shown to improve the signs and symptoms of dry eye disease [49] and contact lens discomfort [50]. In a multicentre, open-label, one year study, 2% rebamipide ophthalmic suspension instilled 4 times daily led to an improvement in fluorescein corneal staining, lissamine green conjunctival staining, and tear film break-up time starting from the 2 week visit, suggesting a relatively rapid rate of action [42]. It has also been used off-label to treat alkali burns [51] and in those with vernal and allergic keratoconjunctivitis [52] and chronic graft-versus-host disease-related dry eye disease [53]. Further, rebamipide has been shown to increase the number of goblet cells in the lid wiper region and to increase the expression of the cell surface proteins, epidermal growth factor [40], MUC16 and MUC5AC [54]. This is significant, as goblet cell damage in the region of the lid wiper may lead to an increase in friction due to a reduction in mucin which can potentially be alleviated by rebamipide [40]. Rebamipide has further been found to decrease markers of inflammation such as IL-8, eosinophil cationic protein (ECP) and total IgE, suggesting that this secretagogue could also help address ocular surface inflammation induced by dry eye disease [55].

Other experimental products which may directly or indirectly affect mucin secretion have been investigated at various stages. **JBP485**, a placental extract-derived dipeptide that has previously been shown to exhibit protective properties for liver and gastrointestinal cells and to have anti-apoptotic and anti-inflammatory effects has since been shown to promote the expression of secretory mucin MUC5AC and of cell-surface associated mucins MUC1, 4 and 16 in the rabbit corneal epithelium [56]. **Mycophenolate mofetil** is an immunosuppressive drug containing mycophenolic acid, a selective inhibitor of inosine monophosphate dehydrogenase which leads to inhibition of the de novo pathway of nucleotide synthesis and at low doses promotes goblet cell proliferation [57–60]. **DA-6034** is an eupatilin derivative of flavonoid which has been shown to be protective of gastric mucosa [61,62] and shown to increase mucin and aqueous secretion and to down-regulate matrix-metalloproteinase-9 (MMP-9) and mitogen-activated protein kinase (MAPK) in an animal dry eye model. Each of these molecules are still early in development and evaluations in large scale clinical trials have yet to be conducted.

Lipid stimulation

Growth factors play an important role in the maintenance of ocular surface homeostasis. **Insulin-like growth factor 1 (IGF-1)** is a potent activator of the phosphonositol 3-kinase (PI3K)/Akt pathway, which stimulates cell proliferation and differentiation while inhibiting apoptosis [63]. As such, IGF-1 receptor (IGF-R) inhibition is one mechanism used to treat cancer [64]. The role of IGF in dry eye has been postulated based on adverse events from clinical cancer trials. In a phase 1 study of figitumumab, an anti-cancer drug that prevents IGF-1 from binding to its receptor, dry eye was its most commonly reported adverse event [65], leading Ding and Sullivan to hypothesize that the inhibition of IGF-1 further inhibited the function of meibomian gland epithelial cells [66]. IGF-1 has been reported to stimulate cellular proliferation and promote lipid accumulation two-fold when applied to human meibomian glands [66]. The role of insulin in dry eye is supported peripherally by the prevalence of dry eye in patients with diabetes, with 50% of people with diabetes complaining of dry eye symptoms [67–69].

Liu and Ding used immortalized human meibomian gland epithelial cells to test the effect of a combination of azithromycin, a macrolide antibiotic, and IGF-1 on meibomian gland cellular differentiation and lipid accumulation [70], hypothesizing that the two drugs would preserve normal proliferation and promote cellular differentiation and lipid accumulation respectively. They found that the combination increased the levels of lipids accumulating within the glands and modulated their composition, while preserving normal proliferation rate [70], suggesting that these two mechanisms may be additive and may be a promising pathway to stimulate meibomian gland secretion. In rabbit eyes, IGF-1 has been shown to improve dry eye parameters and to promote nerve regeneration following laser in situ keratomileusis [71].

Oral secretagogues

Systemic stimulation of components of the tear film have focused on parasympathomimetics. **Pilocarpine** is a non-selective cholinergic agonist which can stimulate the M3 muscarinic receptors in exocrine glands. It is known to increase aqueous secretion from saliva and sweat glands and can also increase the number of conjunctival goblet cells [72]. It is currently available in 5- and 7.5-mg tablets for oral use. In a multicentre, controlled clinical trial of patients with Sjögren's Syndrome comparing pilocarpine 5 mg given 2 or 4 times a day, the higher dose significantly improved dry eye symptoms, while the lower dose performed no differently to the placebo, with patients still experiencing excessive sweating as a commonly reported side effect in both groups [73]. Further, a 12-week randomized controlled study, also in patients with Sjögren's Syndrome, comparing a 5-mg pilocarpine dose taken twice daily to artificial tears or inferior punctal occlusion, an improvement in conjunctival staining was shown with pilocarpine, as well in global assessment of dry eye symptoms, but no difference was found in tear volume as measured by Schirmer test [74]. The significant side effect profile of systemic pilocarpine including excessive sweating and gastrointestinal distress typically render its use only in Sjögren's Syndrome patients.

In contrast to pilocarpine, **cevimeline hydrochloride** is an orally administered derivative of acetylcholine with a 10-fold higher ratio of specificity for M3 rather than M2 receptors, leading to lower potential for cross-stimulation of cardiac and pulmonary receptors than pilocarpine [75]. Stimulation of M3 receptors located in the lacrimal and salivary glands by the drug increases exocrine gland reception [76–78]. The drug has been shown prospectively in Sjögren's Syndrome patients to improve both Schirmer's test scores in 4 and 12 week trials [79,80].

Novel targets of inflammation

Lymphocyte function-associated antigen-1 antagonists for dry eye

As part of both the original and revised definitions of dry eye by the TFOS DEWS I and II, the critical role that inflammation plays in the dis-

ease pathogenesis was highlighted [1,81]. Pharmaceutical management of the disease has thus included agents aimed at suppressing the inflammatory cascade [3]. Topical corticosteroids are potent anti-inflammatories and can have immediate effects on improving signs and symptoms of dry eye, but have limited long term utility due to known risks of secondary infection, rise in intraocular pressure and cataract formation [3]. Alternative anti-inflammatory agents which can be more safely used long term such as topical cyclosporine A have thus been developed. Topical cyclosporine was the first Food and Drug Administration (FDA) approved agent with an indication to manage dry eye by improving tear production affected by ocular inflammation [82]. More recently, **lifitegrast**, the first entry in a class of drugs known as lymphocyte function-associated antigen-1 (LFA-1) antagonists, has been approved by the FDA in 2016 and by Health Canada in 2018 to specifically manage both signs and symptoms of dry eye [83], with its purpose being to minimise the impact of inflammation and hence the propagation of the vicious circle of dry eye disease [2].

Lifitegrast (known during development as SAR 1118) is an antagonist of LFA-1 [84]. The LFA-1 receptor is expressed on T-cells and plays a critical role in facilitating migration from blood vessels to sites of inflammation. Interaction of T-cells with inflamed tissues facilitated by LFA-1 amplifies inflammatory signalling pathways through cytokine release while also promoting further T-cell migration and proliferation [85]. LFA-1 exerts these functions through interaction with its ligand, intracellular adhesion molecule 1 (ICAM-1), which is not only expressed on the endothelium of inflamed blood vessels, but also on antigen presenting cells and epithelial cells during inflammation [83,85]. The prevention of LFA-1 and CAM-1 interaction by lifitegrast presumably reduces further T-cell mediated inflammation [86]. Lifitegrast was specifically designed in the laboratory to be a small molecule to mimic the critical binding sites of ICAM-1 and outcompete the endogenous molecule so that interaction between LFA-1 and ICAM-1 would be minimized [85]. Lifitegrast is highly water soluble and a 5% (50 mg/mL) ophthalmic solution commercially available (Xiidra™, Shire Pharmaceuticals). Twice a day, chronic instillation of the preservative free formulation does not appear to demonstrate any appreciable or unexpected accumulation of the drug in the plasma or tear film [87]. Lifitegrast concentrations within the tear film rise quickly to ocular therapeutic concentrations, reaching a maximum concentration within 0.3 h [88].

There have been four key clinical studies which have been used to support lifitegrast's regulatory approval for release to the market, a Phase 2 trial and three Phase 3 trials (OPUS-1, OPUS-2 and OPUS-3) [89–92]. In combination, the four clinical trials were able to sufficiently demonstrate improvement in both the signs and symptoms of dry eye [83]. Lifitegrast was the first agent to gain this broader indication, as cyclosporine A was previously only indicated to improve the sign of decreased tear production associated with dry eye inflammation [93]. As part of a Phase 2 trial, 0.1%, 1% and 5% lifitegrast solutions demonstrated improved change in inferior corneal staining scores compared to vehicle in a dose dependent manner, leading to the 5% concentration being selected for further Phase 3 trials [89]. In OPUS-1, participants were randomized to 5% lifitegrast or vehicle control for use two times a day over the course of 12 weeks. Inclusion criteria for OPUS-1 included a history of dry eye disease, artificial tear use in the past 6 months, conjunctival redness, corneal fluorescein staining, unanesthetized Schirmer measuring tear production greater than 1 mm but less than 10 mm, and an adverse change in corneal staining and ocular discomfort scores when exposed to a controlled adverse environment [90]. The controlled adverse environment involves a 90-minute session in an environment with controlled temperature, air flow, humidity and lighting designed to exacerbate dry eye signs and symptoms [90]. Requiring a response to the controlled adverse environment for inclusion in the study by the authors was said to ``enrich'' the study population by identifying those most likely to be responsive to changes. After 84 days and examination of 588 patients, 5% lifitegrast was demonstrated to significantly change the inferior corneal staining scores, the defined primary objective sign of dry eye disease, but failed to demonstrate a significant change in its co-primary subjective measure, the vision related function subset score of the Ocular Surface Disease Index [90]. While OPUS-1 was unable to demonstrate improvement in their primary symptom measure, the authors considered the replication of improvement in staining score seen in the Phase 2 trial to provide robust evidence of the efficacy of the drug in managing signs of dry eye. The follow up studies, OPUS-2 and OPUS-3 were directed by suggestive results from OPUS-1 and the Phase 2 trial for the candidates and subjective measures which would be most responsive to the drug [91,92]. The Eye Dryness Score (EDS), a separate subjective measure of eye dryness, was suggested by the results of OPUS-1 to be beneficially affected by lifitegrast, particularly in patients who had a more recent (30 day) history of using artificial tears and a more moderate to severe dryness symptom score (EDS >40) [91,92]. Inclusion criteria for OPUS-2 and the follow up confirmatory study OPUS-3 thus included both this worse dryness symptom score and artificial tear use as inclusion criteria while removing the CAE response requirement. Interestingly, while both OPUS-2 and OPUS-3 were able to robustly demonstrate a change in measured dryness symptoms as measured by the EDS compared to vehicle placebo, OPUS-2 failed to demonstrate an improvement in ICSS as seen with OPUS-1, the phase 2 study as well as OPUS-3 [91,92]. Depending on the rated severity, significant symptomatic relief was seen within 14 days of 5% lifitegrast administration for moderate to severe symptomatic participants (OPUS-2 and OPUS-3) and by 42 days in mild to moderate disease (OPUS-1) [90–92].

A companion study on the long-term safety of the formulation has been conducted and termed SONATA. This 360-day trial examined ``treatment emergent adverse events'' associated with the 5% solution compared to the vehicle [87]. The majority of the commonly reported adverse effects were all considered to be mild in nature, with the most common local effect being irritation at the site of instillation, and the most common systemic effect being dysgeusia [87,90–92]. Overall, use of the drops twice a day does not appear to have any long term local or systemic effects, nor was there any evidence that the long-term immune suppression caused any increased secondary infections.

Summary and future research

There are multiple avenues in which aspects of the pathogenesis of dry eye disease may be targeted by current and developing treatments. Agents to encourage the secretion or restoration of different portions of the tear film are available in different parts of the world or are still within the developmental phase. The challenge may be in the identification of the most appropriate patients for the restoration of deficiencies exerted by the discussed agents. In the management of dry eye-associated inflammation, the development of lifitegrast represents a unique ocular drug development as the agent was specifically designed to manage the ocular disease and provides a road map for the levels of evidence from clinical trial data needed to get the drug to the market through North American regulatory agencies.

The challenge with dry eye continues to be its multifactorial aetiology and lack of concordance in many instances between signs and symptoms of the disease leading to difficult drug development pathways and clinician confidence in reliable management strategies. Treatment success is often focused on certain signs or measures of symptoms whose validity in serving as a correlate for the disease may vary between people. Implementation of the TFOS DEWSII diagnostic and monitoring paradigms represents the current best synthesized evidence in this process and as it becomes implemented into practice its ability to provide reliable information will be constantly evaluated.

Well-designed trials combining different targets of dry eye treatment have also not yet been conducted and so the synergy or additive effects of treatments remain theoretical or based solely on clinical experience. This may present a future avenue of research potential to discover the most appropriate combination to most reliably manage the greatest number of patients.

Conflict of interest

None.

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Submission declaration

This work is original, has not been published and is not being considered for publication elsewhere. There are no conflicts of interest for any of the authors that could have influenced the results of this work. Both authors have contributed significantly to the project and subsequent drafting, revising and approval of the final version submitted.

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