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REVIEW

New advances in medical management of dry eye: optimizing treatment strategies for enhanced relief

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Abstract

Purpose Dry eye disease (DED) is a prevalent ocular surface disease that is conventionally characterized by tear film hyperosmolarity and instability. This review presents a summarized classification of DED, followed by a comprehensive discussion of the most recent topical and systemic medications and clinical recommendations for selecting the most appropriate option for each patient.

Methods An extensive literature search was conducted on electronic databases, such as PubMed, Scopus, and Web of Science, using keywords including "dry eye syndrome," "ocular surface disease," "medical management," "artificial tears," "topical immunomodulators," and "meibomian gland dysfunction."

Results The underlying reasons for DED can range from insufficient aqueous tear production to increased tear evaporation. Recent literature has provided a more in-depth understanding of the pathophysiology of DED by examining the tear film's lipid, aqueous, and mucin layers. However, despite these advancements, medical management of patients with symptomatic DED has not fully reflected this modernized knowledge of its pathophysiology.

Conclusion To develop a rationalized strategy for treating DED, it is crucial to have updated knowledge of therapeutic options, their mechanisms of actions, and indications based on the DED type and underlying causes.

Keywords Artificial tears · Dry eye disease · Evaporative dry eye · Medical management · Mucin secretagogue · Topical immunomodulators

Introduction

Dry eye disease (DED) is a commonly encountered ocular condition, with a prevalence rate of up to 50% in specific populations [1]. It is linked with a substantial population burden, resulting in compromised vision-related quality of life that surpasses any other vision-threatening eye disease [2]. Furthermore, DED imposes a substantial burden on mental health-related quality of life, which is particularly noticeable in cases of undiagnosed and severe DED [3]. As per a recent survey conducted in the United Kingdom (UK), untreated DED has been linked with a significant negative impact on work productivity and visual activities [4]. From an economic standpoint, the estimated cost of managing DED in the United States

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(US) was reported to be 3.8 billion USD, with a societal cost of over 55 billion USD [5]. The per capita cost associated with DED management ranges from 265 to over 1100 USD in European countries and China [6, 7]. Indirect costs constitute the largest proportion of the overall cost attributed to DED [8].

The reduction of the visual, mental, and economic burden of DED on both patients and society can be achieved through accurate diagnosis and effective medical and surgical treatment. This article aims to provide a comprehensive review of the medical treatment of DED with a focus on recent updates concerning topical and oral medications. Conservative therapy is the first line of management for DED, and surgical interventions are generally reserved for severe and refractory cases. As such, updated knowledge of medical treatment is essential for improving the quality of ophthalmology practice for the majority of DED patients.

Pathophysiology

The lacrimal functional unit (LFU) is a comprehensive, unified system that comprises the ocular surface, lacrimal glands, meibomian glands, ocular surface nervous system, and the eyelids [9]. The primary output of the LFU is the tear film [10]. Its lipid layer, which constitutes the outermost layer, is generated by the meibomian glands, whereas the intermediate aqueous sheet and the innermost mucin layer are produced by the lacrimal gland and conjunctival goblet cells, respectively [11]. All layers are integrated to give the tear film certain properties for lubrication, nutrition, protection, repair and transparency of the ocular surface [12].

Tear film instability, which is a characteristic feature of DED, arises from alterations in the quantity or quality of the aqueous, mucin, and lipid layers of the tear film [13]. Upon establishment, tear film instability is primarily characterized by the hyperosmolarity of tears, leading to the induction of inflammatory mediators such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) and resulting in damage to the ocular surface [14]. In cases of DED, the osmolarity of the tear film is elevated to approximately 360 mOsm/L, as opposed to the typical levels of around 300 mOsm/L [12]. Hyperosmolar environment of the ocular surface has also a direct apoptotic effect on the epithelial cells, which is mediated by mitogen-activated protein kinases (MAPKs), chemokines, and different proteinases [15]. Accordingly, the vicious cycle of DED involves a series of interrelated events. It begins with tear hyperosmolarity, leading to ocular surface inflammation, impairment of the epithelial layer, exacerbation of tear film instability, and eventually further elevation of tear film hyperosmolarity [10, 14].

Classification of DED

Drawing on the key role of tear film hyperosmolarity in DED, the condition can be categorized based on the underlying cause of hyperosmolarity, namely "aqueous deficient type," characterized by reduced tear secretion, and "evaporative type," marked by increased tear evaporation [10, 16]. These factors may intersect and both play a role in the pathophysiology of DED. Recent evidence suggests that evaporative tear film instability occurs more frequently than a combined mechanism [11], and aqueous deficient DED alone is the least common type [17].

Aqueous deficient DED

In this particular DED type, the rate of tear film evaporation is normal, but there is a reduction in the secretion of tear from the lacrimal glands. Hyposecretion of the lacrimal glands can occur in various conditions. Intrinsic non-immune dysfunction of the lacrimal glands commonly occurs in older females due to decreased androgenic hormone levels, which contribute to lower tear production [18]. Systemic medications, such as beta blockers, antidepressants, anti-anxiety agents, antihistamines, diuretics, and decongestants, are also linked to decreased secretion [19]. Immune dysfunction of the lacrimal glands is characterized by the infiltration of immune cells and subsequent destruction of secretory units. This pathophysiology is observed in various conditions, including Sjogren's syndrome, rheumatoid arthritis (RA), autoimmune thyroid disease, and hematopoietic stem cell transplantations complicated by chronic graft-versus-host disease (GVHD) [11, 20]. Aqueous deficient DED of the severe cicatrizing conjunctivitis type is characterized by obstruction and scarring of the lacrimal duct, which impedes the delivery of

produced tear to the ocular surface. Several diseases such as Stevens–Johnson syndrome (SJS), severe atopic conditions, ocular mucous membrane pemphigoid (MMP), and trachoma are the main causes of this type of DED [21]. The normal functioning of corneal nerves is essential for the production of tears from lacrimal glands. They are also involved in maintaining the homeostasis of the epithelial layer and immune regulation of the ocular surface [22]. Herpetic keratitis, systemic neuropathies (such as diabetes mellitus), and certain types of ocular surgery (e.g., laser-assisted in situ keratomileusis [LASIK]) can cause damage to these nerves. Such damage is associated with chronic hyposecretive DED [10, 20].

Evaporative DED

This type of dry eye disease is characterized by normal lacrimal secretion, but excessive evaporation of tears, leading to a reduction in water content and an increase in tear film osmolarity. The primary underlying cause of this type of dry eye is insufficient or abnormal production of lipids [16]. Meibomian gland dysfunction (MGD) or blepharitis leads to qualitative and quantitative alterations in the lipid layer of the tear film, resulting in excessive evaporation and subsequent hyperosmolarity of the tear film [23]. Lagophthalmos, incomplete blinking and exophthalmos can lead to increased tear film evaporation and ocular surface exposure, resulting in evaporative dry eye. In addition, decreased blinking rate (less than 5 blinks/second) seen in conditions like Parkinson's disease or Bell's palsy is also associated with this type of dry eye [24]. Prolonged use of digital screens, or visual display terminals (VDTs), is a growing etiology for evaporative DED due to decreased rate of blinking [25]. Besides modern work requirements, an increase in screen time has been observed after recent viral pandemics, which has been reported to increase the incidence of evaporative dry eye and ocular asthenopia [26].

The Asia Dry Eye Society (ADES) has proposed a new classification that distinguishes mucin deficiency from evaporative dry eye, which they call "decreased wettability dry eye." This differs from the previous classification suggested by the Tear Film and Ocular Surface Dry Eye Workshop (TFOS DEWS) II report, which includes mucin layer abnormality as a cause of evaporative dry eye [27]. The underlying mechanism of decreased wettability DED involves the shortage of membrane-associated mucin or mucins synthesized by conjunctival goblet cells, which disrupts the corneal surface's ability to remain wet. This deficit in the effective mucin layer results in the amplification of tear evaporation and an increase in tear hyperosmolarity [28]. Mucin deficiency DED is commonly associated with conditions such as contact lens use, chronic allergic conditions, benzalkonium chloride (BAK) toxicity, and vitamin A deficiency [28]. Use of both rigid gas permeable and soft contact lenses are shown to reduce goblet cell density and mucin production over 6 months [29, 30]. Exposure to BAK, especially in patients receiving long-term antiglaucoma agents, is associated with tear film instability, loss of goblet cells, and evaporative DED [31]. Whether through BAK or the active ingredient of the drops, mucin deficiency and goblet cell loss seem to have the pivotal roles in glaucoma-associated ocular surface disease [32].

Diagnosis of DED

The symptomatology of DED is not sufficient to differentiate it from other possible diagnoses or to identify the type of DED. Therefore, a comprehensive patient history and standard ophthalmic examinations are the primary approaches for diagnosing and classifying DED. A comprehensive assessment of the patient's history should include a review of any ocular surgeries, recent or prolonged use of topical medications, contact lens usage, atopy or allergic conjunctivitis, and systemic diseases or medications. Additionally, any occupational or environmental factors that may predispose the patient to DED, such as prolonged desk work or dry and hot weather, should be taken into account.

Aberrant patterns of blinking can provide important insights into the diagnosis of DED. A reduced blink rate is associated with an increased risk of evaporative DED, whereas an increased blink rate can be an indicator of ocular surface dryness in cases where reduced blink rate is not the primary cause of DED [33]. The measurement of tear meniscus height can be a useful diagnostic tool for DED, especially when other clinical tests are not available or feasible. The measurement of tear meniscus height can be obtained using Keratograph 5M or optical

coherence tomography (OCT) [34]. A recent report has approved the efficacy of the new strip meniscometry (SM) in the diagnosis of dry eyes [35].

Lid-parallel conjunctival folds (LIPCOFs) are another sign used by 70% of European ophthalmologists to diagnose DED [36, 37]. Quick and noninvasive nature, good positive predictive value, and moderate sensitivity and specificity are advantages of LIPCOFs as a DED screening tool [38].

When DED symptoms are present, corneal staining in inferior zones is the most frequent type of staining and correlates with more severe grades of DED [39]. When assessing corneal staining in diagnosing DED and evaluating its severity, a combination of fluorescein and lissamine green dyes is often preferred. This complementary technique enables fluorescein to reveal de-epithelialized sites with clearer corneal staining, while lissamine green detects earlier epithelial cell damage on both the cornea and conjunctiva [40].

With or without anesthesia, amount of Schirmer paper's wetting (less than 10 mm over 5 min) is another frequent method for evaluating tear secretion [41]. In recent years, there has been progress in interpreting the Schirmer test results. Weighted calculation of paper wetting during the final 4 min, while decreasing the relative importance of the first minute wetting, may improve the test's sensitivity without requiring anesthesia [42].

Tear breakup time (TBUT) is often utilized to confirm tear film instability in cases where it is less than 10 s. TBUT incorporates both the aqueous and lipid components of the tear film, rendering it a reliable diagnostic test for DED, albeit lacking the ability to distinguish between aqueous deficient and evaporative types. [43] In a recent investigation, a threshold value of 5.3 to 6.0 s was identified as having excellent accuracy in discriminating between normal eyes and those with DED [44].

In order to address the limitations of conventional clinical tests, several ancillary tests have been proposed for diagnosing DED. Tear film osmolarity measurement can confirm tear hyperosmolarity. While it has been validated as a laboratory test for diagnosing dry eye, the interpretation of the result may be challenging due to inconsistent correlation with clinical signs or symptoms [45]. Matrix metalloproteinase-9 (MMP-9) levels are claimed to have the ability to diagnose DED, grade its severity and monitor the treatment response, although it fails to differentiate DED from other inflammatory conditions [46]. Recent studies have indicated that a decrease in lactoferrin levels within the tear film is indicative of reduced lacrimal gland function [47]. The TearScience Inc.'s LipiView interferometer, based on the analysis of the interferometric pattern of the patient's tears, can effectively assess the thickness of the tear film lipid layer [48].

Conservative non-medical treatments of DED

The therapeutic approach to DED involves a sequential process, beginning with conservative non-pharmacological measures such as lifestyle adjustments, environmental modifications, and occupational interventions. Existing literature primarily emphasizes conservative therapy for general ocular surface symptoms, regardless of the DED subtype. Such interventions are typically reserved for DED prevention or the management of mild symptoms. Nonetheless, they should not be disregarded as complementary therapy to pharmacological treatments in the more advanced stages of DED.

Weight loss, decreased calorie intake, and restriction of sedentary behaviors have been recommended to improve DED symptoms [49]. Adopting a Mediterranean diet (e.g., low intake of dairy and meat and high intake of fish, nuts, and olive oil), in addition to increasing physical activity, has been recently suggested to control DED symptoms in general [50]. Increased dietary intake of fruits and vegetables rich in quercetin and other anti-oxidant molecules has also been associated with promising results in improving tear film function [51].

Air moisturizing in warm climate and low humidity environments may have beneficial effects on the tear film [52]. In a clinical trial on 30 patients, moisture chamber spectacles were a safe and effective treatment for DED, especially for patients who live in environment with low humidity [53]. In another study, temporary use of the warming moist chamber goggles was successful in relieving MGD- and VDT-associated DED symptoms in short-term [54]. According to reports, the use of moist cool air devices has also demonstrated symptomatic improvement in office workers with DED [55]. Generally, air moisturizing devices, chambers, and goggles may serve

as a promising alternative therapy for mild DED in patients residing in unfavorable environmental and climatic conditions. Moreover, to mitigate tear film evaporation, it is commonly advised to avoid exposure to cold winds during winter and direct airflow from air conditioning units during summer.

Occupational risk factors associated with prolonged use of VDTs and computer vision have been addressed by implementing ergonomic modifications such as adjustable chairs and frequent breaks, as well as utilizing blinking animation programs [56]. These modifications aim to mitigate the risk factors associated with evaporative DED by increasing blink rate and reducing screen time.

Main determinants of medical management strategies for DED

Accurate determination of DED type and grading of DED severity are essential prerequisites to initiating appropriate treatment with the correct use of available products. Knowledge of the specific DED type will enable the adoption of a tear film-oriented strategy, wherein the most affected layer, whether aqueous, mucin, or lipid, is targeted for treatment of DED. Assessing the severity of DED is an additional strategy, given that severe cases may require a multidrug approach to prevent complications that could threaten vision.

Determination of DED type; tear film-oriented strategy

The presence of superficial punctate keratopathy, reduced strip meniscometry (less than 4 mm in 5 s), abnormal Schirmer strip test without anesthesia (less than 5 mm in 5 min), and reduced LIPCOF indicate the likelihood of aqueous deficient DED [27, 35, 57]. According to the compensatory theory, aqueous deficiency in DED may be linked to increased mucus production from goblet cells and a thicker lipid layer due to MGD [58]. These changes may contribute to the development of filamentary keratopathy. Additionally, the decreased fluid volume in these patients may result in delayed tear film clearance, leading to mucus accumulation and a thicker lipid layer [27]. Observation of the tear breakup pattern reveals the appearance of line breaks on the inferior cornea upon redistribution of fluorescein-stained tears following eye opening [59]. The replacement of the aqueous component of the tear film is crucial in the treatment of aqueous deficient DED. This can be accomplished through the use of artificial tears (AT) and aqueous secretagogues. In cases where inflammation is the central mechanism of DED-related damage, anti-inflammatory agents should be considered to control inflammation when necessary.

Pathological observations of meibomian gland orifices or the eyelid margin are indicative of evaporative DED. Thinning of the lipid layer, as observed through lipid layer interferometry, suggests lipid deficiency and the presence of evaporative DED [12, 48]. In cases of pure lipid deficiency DED, the presence of normal mucin leads to the appearance of random breaks in the tear breakup pattern [27]. In cases where pure lipid deficiency DED is present, treatment should primarily target the lipid layer. This involves addressing MGD to improve the quality and quantity of meibum, which facilitates lipid layer replacement. ATs can be used to replace evaporated tears, and lipid-containing tear substitutes and ophthalmic ointments can be utilized to temporarily enhance the diminished lipid layer [60].

Proposed characteristics of decreased wettability DED include a short TBUT of nearly 0 s, along with the presence of spot or dimple breaks in the tear breakup pattern immediately following eye opening [59]. The lack of an appropriate response to typical DED medications and the absence of corneal staining during examination are additional features indicative of mucin deficiency DED [27]. Tear substitutes that contain mucomimetic material may be particularly beneficial in the treatment of patients with mucin deficiency DED. Additionally, newer mucin secretagogues may also be a promising option for managing this type of DED [28]. In addition, as an alternative approach, mucin-like agents such as lubricin can be utilized to replace lost mucins on the ocular surface [61].

Grading DED severity; severity-based strategy

The grading process of DED typically commences with an assessment of the patient's reported symptoms (Table 1). DED questionnaires and patient-reported outcomes (PROs) are well-known tools for

evaluation and grading of symptoms [62]. According to a review in 2020, 24 DED questionnaires have been suggested in ophthalmic literature, among them the Ocular Surface Disease Index (OSDI), impact of dry eye in everyday life (IDEEL), dry eye-related quality-of-life score (DEQS), National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ25), and University of North Carolina Dry Eye Management Scale (UNC DEMS) are more recommended based on their attention to quality of life parameters [63]. Dry eye questionnaires have been developed for various purposes and in different languages, emphasizing the importance for clinicians to carefully select the appropriate questionnaire based on the specific clinical situation of the patient.

Various DED severity classification systems also incorporate clinical tests such as corneal staining, TBUT, Schirmer test, and the presence and severity of MGD as important factors to determine the severity of DED. Combining symptom evaluation and clinical tests, various DED severity classification systems have been suggested in the literature, including the triple classification of dry eye for practical clinical use [64], the Dysfunctional Tear Syndrome Study Group [65], TFOS DEWS I Report [66], the ODISSEY European Consensus [67], the Italian Dacryology and Ocular Surface Society Classification [68], and the Mexican Dry Eye Disease Expert Panel [69].

Despite the variations in DED severity classification systems, some general rules can be identified regarding the role of DED severity in medical treatment strategies. Patients with mild disease can be managed using lubricant eye drops that are currently available. Preserved ATs may be an acceptable option for lower frequency treatments; however, if treatment is scheduled for long-term use, preservative-free (PF) ATs are preferred [11]. Modification of lifestyle is also advised, including smoking cessation, reduction of screen time, identification of exacerbating factors such as systemic medications, and humidification of ambient air [71, 72]. In all grades of DED, special attention should be given to concomitant conditions, particularly MGD and blepharitis.

In moderate DED cases, most classification systems recommend the addition of topical anti-inflammatory agents to the previously mentioned treatment options. A variety of anti-inflammatory agents can be utilized, ranging from corticosteroids to cyclosporine A (CsA) and lifitegrast [73, 74]. Adjunctive therapy with fatty acid supplement (omega-3) is also considered in moderate DED [75]. Due to the need for more aggressive lubricating therapy, PF drops are preferred over preserved AT in this stage of DED treatment [11]. Moderate to severe DED patients are often prescribed topical secretagogue agents to stimulate the secretion of mucin [76].

In severe cases of DED, oral cholinergic agonists, autologous serum drops, and platelet-rich plasma (PRP) are frequently recommended [77]. The presence of filamentary keratitis should be noted in this stage as it requires specific therapeutic interventions. Topical corticosteroids may be required for a

Table 1 Representative symptoms and signs of mild, moderate and severe DED according to different classification systems. Abbreviation: DED, dry eye disease; TBUT, tear break-up time

Severity of DED	Symptoms (dryness, foreign body sensation, redness, ocular burning)	Signs (conjunctival staining, corneal staining, reduced TBUT, reduced Schirmer test, reduced tear meniscus, conjunctival scarring, eyelid margin alteration)	Permanent vision loss
Mild	Episodic/intermittent[66, 68, 70]	No corneal damage[65, 67] No/mild tear signs[66, 67] Mild to moderate conjunctival staining[65, 66]	No
Moderate	Frequent[66]	Peripheral/reversible corneal damage[65, 67] Moderate tear signs[66, 67] Severe conjunctival staining without scarring No eyelid margin alteration	No
Severe	Frequent[68, 70]	Central/irreversible corneal damage[65] Filamentary keratitis[65] Severe reduced tear signs[66] Conjunctival scarring[65–68] Altered eyelid margins[66]	Yes[70]

prolonged period in severe DED. Occasionally, systemic anti-inflammatory medications may be used to control DED and concomitant systemic immune condition [78].

Medical treatment of DED; an update on options

The primary components of medical management for DED include tear substitution, anti-inflammatory therapy, mucin substitution through the use of mucin secretagogues, and treatment of MGD (Table 2).

Tear substitution

Tear substitution is an established therapeutic strategy for managing DED symptoms. ATs are commonly used to replace and supplement the inadequate natural tear film. However, recent advances in tear substitution therapy have led to the development of novel formulations such as liposomal sprays. Furthermore, biological tear substitutes, such as autologous serum eye drops, have emerged as a promising therapeutic option for severe and refractory cases of DED.

Artificial tears

The primary medical management approach for DED involves the use of AT drops, gel-type drops, gels, and ointments. These interventions are considered first-line therapy [79]. ATs are widely used in the management of all stages and types of DED. These products typically contain a combination of key ingredients, including demulcents, electrolytes, emollients (oily agents), and preservatives. The primary objective of ATs is to lubricate the ocular surface and augment the volume of the aqueous tear film through the use of water-soluble polymers known as demulcent agents. In addition to their lubricating properties, ATs are known to decrease tear film hyperosmolarity and dilute the concentration of inflammatory mediators, which can help to alleviate the inflammatory process associated with DED [13].

When prescribing ATs for patients with DED, clinicians must take several factors into consideration to ensure optimal treatment outcomes. When ATs are required more than four times a day, PF ATs are generally recommended to avoid potential toxicity associated with the prolonged use of preservatives [12]. Single-dose preparations of ATs are available that do not contain BAK or other preservatives. A recent meta-analysis of four studies evaluated the efficacy of preserved and PF ATs in reducing signs and symptoms of DED. The analysis did not identify a significant difference in efficacy between the two types of ATs [80]. Accordingly, the primary advantage of PF ATs over preserved formulations is their superior safety profile and lower incidence of adverse effect.

The main methods for increasing the viscosity of ATs involve increasing the concentration of demulcent agents, using multiple demulcents in the formulation, or incorporating high-molecular-weight demulcents. By enhancing the viscosity of the tear film, these techniques can improve the lubricating properties of ATs and prolong their retention time on the ocular surface [81]. For patients with moderate to severe DED, higher viscosity formulations are often

Table 2 Available medical treatments of DED based on pathophysiologic aspects

Pathophysiology-based treatment of DED		
Tear substitution	Anti-inflammatory treatment	Mucin substitution
Artificial tears	Corticosteroids	Diquafosol tetrasodium
Liposomal sprays	Cyclosporine A	Rebamipide
Intranasal sprays	Tacrolimus	Vitamin A
Autologous serum	Lifitegrast	Lubricin
Platelet-rich plasma	Non-steroid anti-inflammatory drugs	
Plasma rich in growth factor	Essential fatty acids	
Umbilical cord blood serum		
Human serum albumin		
Nerve growth factor		
Amniotic membrane extract		

preferred [82]. Mid-viscosity gel-type tears provide the advantages of increased viscosity while being easier to apply compared to gels and ointments. This is particularly beneficial for nighttime use when application may be more difficult. In clinical practice, gel-type ATs have been found to provide greater improvements in both signs and symptoms of DED compared to standard low-viscosity drops [83].

Hyaluronic acid (HA) and its sodium salt derivative can serve multiple purposes in treating DED, including increasing water retention on the ocular surface, reducing inflammation, controlling excessive evaporation, enhancing meibomian gland function, and improving the homeostasis of epithelial and goblet cells [84]. Based on its multifunctional properties, ATs containing HA may be the preferred choice for clinicians treating severe and mixed-type DED. A meta-analysis of 19 studies found that HA eye drops were more effective than non-HA ATs in improving both the signs and symptoms of DED [85]. The utilization of high molecular weight HA (HMW-HA) has demonstrated additional benefits in both in vivo and in vitro studies. Studies have shown that compared to low molecular weight (LMW-HA), HMW-HA may result in greater improvements in DED signs and provide better protection of epithelial cells [86].

To compensate for the lipid layer deficiency in DED, some ATs are formulated with emollients or surfactants, such as flaxseed oil, castor oil, dimyristoyl-phosphatidylglycerol, and cetalkonium chloride (CKC), which are claimed to increase the thickness of the tear film lipid layer and improve patient comfort [87]. These types of ATs may be preferred for evaporative DED and MGD patients. Similar to the lipid layer, specialized ATs are available that can restore the mucin layer through the inclusion of carbomers and hydroxypropyl-guar (HP-guar) [28]. These agents possess a branched molecular structure, which enables them to imitate mucin-1, the natural product of goblet cells, and provide ocular surface protection through their mucoadhesive function [88].

Some ATs contain osmoprotectants, which are agents aimed at protecting epithelial cells from damage caused by tear film hyperosmolarity in DED. Trehalose is one of the osmoprotectants that has been suggested to be effective in treating moderate to severe DED when added to AT, as compared to saline [89]. L-carnitine, erythritol, betaine, sorbitol, and glycerin are other osmoprotectants used in AT manufacturing [90]. Some formulations may also include antioxidants, as oxidative stress has been linked to inflammation and tissue damage in DED [90]. These formulations may contain taurine, vitamin A, epsilon amino caproic acid, vitamins E, B6 and B12 to provide antioxidant properties and protect ocular surface epithelial cells from oxidative stress [90, 91].

Liposomal sprays

Several studies have confirmed the effectiveness of liposomal sprays, which contain spherical vesicles of phospholipids with an embedded aqueous component, in treating signs and symptoms of DED [92]. These sprays are sprayed over the closed eyelids and are absorbed onto the ocular surface from the eyelid margin through blinking. They have been found to improve TBUT, Schirmer test results, and LIPCOFs [93, 94]. A study compared four available sprays and found all effective in treating DED, with Ocuvers spray (Ocuvers, Innomedis AG, Germany) group showing greater improvement in signs and symptoms [95]. A recent improvement in liposomal spray production involves increasing phospholipid concentration in the liposomal content, as shown in a recent study where a high-concentration phospholipid spray improved tear film stability and ocular comfort [96]. Another study investigated the combination of liposomes with osmoprotectants, electrolytes, and viscosity-enhancing agents to create a formulation more similar to normal tear film [97]. Future trials are needed to further evaluate the role of liposomal sprays in the treatment of DED, despite the promising preliminary results.

Nicotinic acetylcholine receptor (nAChR) agonist nasal sprays

nAChR agonists, such as varenicline (OC-01) and simpinicline (OC-02), activate the nasolacrimal reflex to increase tear secretion. They are administered as nasal sprays, offering advantages over topical drops by bypassing the ocular surface and reducing local adverse effects of preservatives [98]. These solutions can be used for various DED types and may become

valuable adjunctive options for patients with multiple drop regimens.

The ONSET-2 clinical trial (Efficacy and Safety of OC-01 Nasal Spray on Signs and Symptoms of Dry Eye Disease) led to the approval of Tyrvaya® (Oyster Point Pharma, NJ, USA) as a varenicline solution nasal spray for the treatment of DED [99]. A 50 µL intranasal spray was administered twice a day in each nostril. The study showed that the spray was effective and safe in treating symptoms and signs of different DED types [99]. In the MYSTIC study, which was a phase II randomized trial to evaluate the long-term efficacy and safety of OC-01 nasal spray for dry eye disease, participants received intranasal varenicline spray twice daily for 84 days. The treatment improved objective measurement of tear film production over a longer period of time, and no serious adverse effects were reported [100]. The efficacy and safety of simpinicline intranasal spray in DED was evaluated in the PEARL study (clinical trial to evaluate the efficacy of OC-02 nasal spray on signs and symptoms of dry eye disease). The treatment consisted of a single dose in-office treatment administered at first and second visits with an interval of 2–3 weeks, and it successfully provided rapid relief of DED symptoms without serious adverse effects [101].

Blood-derived products

Severe cases of DED often require the substitution of tears with biologic fluids. Autologous serum drops, platelet-rich plasma (PRP), and umbilical cord blood serum (UCBS) are examples of such fluids, which contain growth factors, albumin, lactoferrin, immunoglobulin, vitamins, and enzymes [11].

Autologous serum is rich in various growth factors, including epidermal growth factor (EGF), transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and albumin [102]. The function of autologous serum drops for treating DED is improved in terms of epithelial healing, inflammation control, and symptomatic relief due to the presence of these growth factors [102].

Autologous serum is typically prepared from a patient's own blood at a concentration of 20%, based on the actual concentration of biologic factors in normal tears. However, concentrations of 50% and 100% have also been utilized with positive clinical results [103]. A recent pilot study was conducted to compare the effectiveness of autologous serum drops with allogenic serum drops for patients who cannot donate blood. The study concluded that the efficacy and tolerability of allogenic serum drops were similar to those of autologous serum drops for treating severe DED [104]. The primary challenges of using autologous serum for treating DED involve proper preparation and storage to minimize the risk of contamination [76]. Once the patient's blood is collected and centrifuged, the resulting serum is diluted with saline, and it is advised to store the product in a refrigerator (up to 2 weeks) or freezer (up to 3 months) to ensure appropriate preservation with minimal contamination risk [105]. Autologous serum is a suitable option for managing DED, especially in inpatient settings [106].

From a clinical perspective, a review of 5 trials concluded that autologous serum provided greater short-term symptom control for DED compared to AT [77]. Another meta-analysis of randomized controlled trials conducted in 2019 found that all seven studies included in the review showed that autologous serum was more effective than artificial tears in improving symptoms of DED [107].

PRP is generated to provide a high concentration of platelets in a small amount of plasma, which contains high concentrations of several growth factors (e.g., EGF, PDGF, TGF, and insulin-like growth factor [IGF]). Compared to autologous serum, PRP has been reported to have a higher concentration of biologic growth factors [108]. To be more concise, a recent study showed that PRP had higher concentrations of some growth factors, such as TGF, but lower levels of others, such as PDGF, compared to autologous serum. Fibronectin concentration at baseline was similar between the two, but it increased in PRP after storage [109].

PRP has been found to significantly improve symptoms of moderate to severe chronic DED [110–112]. A study comparing PRP and autologous serum found that PRP was superior in terms of producing greater improvements in symptom scores and visual acuity in patients with DED [109]. PRP preparation has an advantage over autologous serum in terms of incubation time, as it does not require the 2-h incubation period needed for autologous serum preparation [109]. The shorter preparation time required for PRP compared to autologous serum may enhance patient convenience and preference for long-term treatment. As another specific characteristic, storing

PRP (which is allowed for 2 weeks in refrigerator and 3 months in freezer) may lead to activation of platelets and increase growth factor concentration, which may explain why frozen or refrigerated PRP could be more effective than fresh PRP [109, 113, 114].

A recent technique proposed for the treatment of severe DED is the injection of PRP into the lacrimal gland. The technique involves a single injection of 1 ml of PRP through a transcutaneous approach from the outer one-third of the superior orbital rim at a depth of 4 mm [115].

The development of autologous blood-derived products has recently focused on platelet activation or lysis to release growth factors from their vesicles and enhance the concentration of growth factors in the final plasma. To obtain plasma-rich growth factor (PRGF), the patient's whole blood sample is centrifuged similarly to the preparation process for autologous serum and PRP. However, the resulting plasma is activated with calcium chloride to form a clot and release growth factors from the activated platelets [116]. The resulting supernatant plasma is then diluted to 20% with normal saline and can be stored in the freezer for up to 3 months or in the refrigerator for up to 1 week [117].

Administering PRGF four times a day has been found to alleviate symptoms of moderate to severe cases of DED that do not respond to conventional treatments [117]. A recent study showed that PRGF is effective in treating DED and has a better cost-effectiveness profile than autologous serum [118]. PRGF eye drops have shown to be more effective than conventional therapy for improving DED symptoms in eyes that have undergone refractive surgery [119].

Autologous platelet lysate (APL) is a blood derivative produced from PRP, where platelets are lysed through consecutive thermal shocks. This process leads to the release of PDGFs into the plasma [120]. The administration of APL to the ocular surface is expected to enhance tear film stability, reduce inflammation of the ocular surface, and improve the epithelial homeostasis due to the high concentration of PDGFs [121]. Reports have indicated that APL eye drops are effective in the treatment of patients with refractory DED that is secondary to primary Sjögren's syndrome [120]. The efficacy of APL drops has also been assessed in patients with DED that is secondary to GVHD, and due to its anti-inflammatory properties, APL was found to be more effective than conventional treatment in providing symptomatic relief to patients [122].

UCBS has been widely utilized in the context of ocular surface diseases and has demonstrated satisfactory outcomes with regard to both effectiveness and safety [123]. UCBS is considered superior to other blood-derived products in terms of its ability to replace damaged corneal epithelial, endothelial, and stromal cells due to the higher concentration of growth factors as well as the presence of mesenchymal and epithelial stem cells [124]. Studies have indicated that UCBS is more efficacious than autologous serum in managing DED that is secondary to GVHD and Sjogren's syndrome [125, 126]. Topical administration of UCBS, when given 6–10 times a day for a duration of 2 to 6 months, has been found to accelerate the healing process, increase the number of goblet cells, and enhance corneal sensitivity [123]. In addition to treating DED, UCBS has also shown successful outcomes in managing other ocular surface diseases such as persistent and recurrent epithelial defects, neurotrophic keratopathy, and ocular chemical burns [127].

In experimental models, human serum albumin (HAS) reduces apoptosis and inhibits caspase-3 activity over the ocular surface [128]. A clinical pilot study demonstrated that the use of 5% HSA eye drops for a duration of 4 weeks resulted in an improvement in corneal staining, TBUT, and reduction in symptoms associated with DED [129]. A recent study compared the effectiveness of albumin 5% eye drops with HA eye drops in treating severe ocular surface disease, and the results showed that both treatments had similar efficacy [130].

Nerve growth factor (NGF)

NGF is a neurotrophic agent involved in corneal sensitivity, ocular surface healing, and tear film production [131]. Topical administration of recombinant human nerve growth factor (rhNGF) has been recently utilized for managing neurotrophic ulcers and DED due to its various therapeutic effects [132]. Cenegermin® (rhNGF) eye drops received approval from the European Medicines Agency for the management of moderate to severe neurotrophic keratitis [133]. The REPARO study group conducted a Phase I clinical trial to evaluate the safety of rhNGF eye

drops at a concentration of 20 µg/mL for managing neurotrophic keratitis. The study revealed that the treatment had a good safety profile, with eye irritation being the most frequently reported adverse effect [134]. The REPARO phase II study demonstrated the effectiveness of rhNGF eye drops at concentrations of 10 µg/mL and 20 µg/mL, administered six times daily for a duration of 8 weeks, in treating neurotrophic keratitis [135].

A recent clinical trial conducted on patients with DED indicated that both 4 µg/mL and 20 µg/mL concentrations of rhNGF eye drops were effective in improving symptoms and signs of DED [133]. In the trial, patients with moderate to severe hyposecretive DED were treated with rhNGF eye drops twice daily for a duration of 4 weeks. The study reported a rapid therapeutic effect within 1 week of initiating the treatment, which was likely due to the modulation of nerve function and the healing process of the corneal epithelium. This effect resulted in an improvement in DED symptoms and signs [133]. It appears that lower concentrations and less frequent regimens of rhNGF eye drops may be sufficient for managing DED compared to the treatment of neurotrophic keratitis.

Amniotic membrane extract (AME)

The amniotic membrane has a dual role in the treatment of ocular surface diseases. It acts as a scaffold to support the proliferation and migration of ocular surface epithelial cells, while also functioning as an immunomodulatory agent that reduces cytokine release and activation [136]. Clinical and experimental studies have utilized AME eye drops (AMEED) for the treatment of ocular surface conditions such as chemical burns, delayed epithelialization, and DED [137–139]. The preparation of AMEED involves the washing, disinfection, and centrifugation of human placental amniotic membrane. The product type determines whether it can be stored in a freezer or refrigerator and how often it should be used, typically ranging from 1 to 4 times a day for a period of 3 to 30 days [140]. Studies have demonstrated that administering AMEED is a safe and effective method for treating the signs and symptoms of DED [141]. Despite the positive results, the conclusions regarding the efficacy of AMEED in treating DED are limited due to the diversity in manufacturing, storage, and treatment protocols, as well as the insufficiency of controlled clinical trials.

Anti-inflammatory treatment for DED

To prevent and treat chronic DED, controlling inflammation is a critical step. Therefore, in cases of moderate to severe DED, the use of anti-inflammatory drugs is required.

Corticosteroids

Indeed, short-term use of steroid eye drops is considered an effective option for treating acute flares of DED or refractory cases [142]. It should be noted that long-term administration of topical steroids for DED may increase the risk of developing cataracts and glaucoma, regardless of the potency of the steroid. However, low-potency agents like fluorometholone (FML) and loteprednol etabonate (LE), particularly in PF formulations, may have a lower risk of corneal penetration and adverse effects and have been advocated for long-term use in selected cases [143].

Prednisolone drops are available in two formulations, acetate (0.125% and 1% suspension) and phosphate (1% solution). Prednisolone acetate provides a more potent effect compared to prednisolone phosphate [144]. A randomized clinical trial found the superiority of prednisolone acetate 0.1% eye drops used three times a day for 30 days over AT in controlling the signs and symptoms of DED [145]. Dexamethasone can be formulated as a 0.1–0.2% suspension or solution, or as a 0.05–0.2% sodium phosphate ointment [146]. Although concerns exist regarding the risk of intraocular pressure (IOP) rise in DED treatment with dexamethasone, in a case-series on 31 patients treated with PF diluted dexamethasone (0.01%), it was found that 65% of patients showed moderate to complete resolution of symptoms with a minimal rise in (IOP) [147]. Significant improvement in signs and symptoms of DED has been reported with the use of iontophoretically delivered dexamethasone phosphate [148].

Treating DED has been effective with FML suspensions at concentrations of 0.1%, 0.2%, and 0.25%, administered 2–4 times per day for a period of 2–4 weeks [12, 146]. FML is less likely to cause an increase in IOP compared to prednisolone and dexamethasone, which may suggest a safer profile

for long-term treatment of DED [146]. Similarly, low dose hydrocortisone 0.335% has been shown to reduce inflammation and symptoms of DED without any change in IOP [149]. A review of 16 prospective and retrospective studies has found that ophthalmic gel 0.5% or ophthalmic suspension 0.5% of LE are other steroid options gaining notice for having a lower effect on increasing IOP. The review showed that LE was effective, safe, and well-tolerated for treating DED with minimal adverse effects regarding IOP [150]. A study found that both FML 0.1% and LE 0.5% were effective in managing symptoms and signs of DED when applied for a long period of time. However, LE had a lower risk of causing elevation in IOP compared to FML 0.1% [151].

There is limited evidence regarding the efficacy of difluprednate, rimexolone, and clobetasone as topical corticosteroids for treating DED. However, in a clinical trial, clobetasone butyrate 0.1% was shown to improve DED symptoms and corneal and conjunctival staining in patients with Sjögren's syndrome when applied twice daily for one month [152].

Cyclosporine A

CsA is a calcineurin inhibitor able to suppress T-cells and reduce cytokine release in different inflammatory diseases [153]. The effectiveness of topical CsA in the treatment of moderate to severe and refractory DED is well established [154]. Less severe cases of DED have also been treated with topical CsA in clinical practice due to its safer profile compared to corticosteroids [155]. Apart from its immunomodulatory effects, CsA can also prevent apoptosis of conjunctival epithelial cells and enhance the density of goblet cells on the ocular surface [156].

According to a study, CsA 0.05% emulsion has been suggested as a favorable treatment choice for DED after ocular surgeries, as it was found to improve DED symptoms after LASIK for up to 1 year [157]. Similarly, a study reported improvement in symptoms of DED after 3 months of treatment with CsA in patients who had undergone cataract surgery [158]. The effectiveness of CsA in treating surgery-induced DED is based on its ability to increase epithelial cell density, decrease surgical nerve damage, and reduce inflammation markers [159].

CsA 0.05% emulsion is among the available formulations of CsA. Clinical trials have shown that twice-daily application of CsA 0.05% emulsion for a period of 6 months significantly improves signs and symptoms of DED, including corneal and conjunctival staining, TBUT, and Schirmer tear values compared to baseline [160, 161]. Burning and pain at the site of instillation are the most common adverse effects of CsA emulsion, reported in more than 40% of patients [161].

The second formulation of CsA available is an aqueous nanomicellar formulation called OTX-101 0.09% (CsA 0.09%). It has been shown to increase tear production and reduce corneal staining in DED patients as early as 4 weeks after being administered twice daily [162, 163]. Switching from the emulsion formulation of CsA to the nanomicellar formulation has been linked to a shorter delay in achieving an effective response, higher CsA concentration in ocular tissues, and a dose-dependent increase in tissue concentration with repeated administration [164]. As another advantage, nanomicellar solution of CsA delivers therapeutic concentration without significant discomfort to the eye during instillation [165].

The third CsA formulation is a cationic unpreserved emulsion containing CsA 0.1%. It was approved in Europe in 2015 for the treatment of DED in adults [166]. Despite of theoretical advantages, it could not reduce the rate of dysesthesia and stinging sensation over instillation as the main complication of CsA drops (reported in 37% of the cases using cationic emulsion of CsA 0.1%) [167].

Twice daily dosing is the recommended regimen for all formulations of CsA therapy in the treatment of DED [155]. On the other hand, some experts recommend up to four times a day dosage for patients who are unresponsive to the twice-a-day regimen or for achieving a faster clinical response [168]. In cases of more severe DED, increasing the frequency of CsA regimens may lead to improved efficacy without significant systemic adsorption and adverse effects [169]. Increasing the concentration of CsA, however, may increase patient discomfort without providing additional therapeutic benefits [169]. Therefore, it appears that using CsA at concentrations of 0.05 to 0.1% for DED provides the best balance of efficacy and complication status [169].

Studies have indicated that it may take around four to six months for CsA to alleviate DED symptoms [160, 170]. In order to achieve faster relief of symptoms in moderate to severe DED with CsA, some

studies suggest using induction therapy with corticosteroid drops two weeks before starting CsA treatment, or combining topical corticosteroid with CsA. This approach has been shown to provide more rapid and effective symptom relief compared to using CsA alone [171, 172].

To prevent a relapse of symptoms related to DED, it is suggested that CsA be used for an extended duration, and for some patients, indefinite usage may be required [154]. The authors of a study recommended extended maintenance therapy for chronic DED after observing disease progression upon discontinuation of CsA following one year of treatment [173]. After 12 months of treatment, a study suggested that CsA dosage could be safely reduced from twice-daily application to once-daily treatment without compromising treatment efficacy [73].

Tacrolimus

Tacrolimus is another inhibitor of calcineurin phosphatases, which inhibits inflammation through reducing T cell activation [174]. Tacrolimus and CsA differ in their mechanism of anti-inflammatory action as they target different proteins. While CsA binds to cyclophilin, tacrolimus binds to FK506 protein and exerts a calcineurin inhibitory action that is 100 times more potent than that of CsA [175]. Like CsA, topical administration of tacrolimus is often associated with an intense stinging sensation as the main adverse effect. However, many patients can tolerate this sensation without it affecting their adherence to treatment [176].

There is some evidence from studies to suggest that topical application of tacrolimus 0.03% may be useful in the treatment of DED [177, 178]. According to these studies, clinical response to topical tacrolimus 0.03% was observed after 7 days of treatment, and the clinical improvement was seen to continue over a period of 3 months [179]. A comparison of the efficacy of twice-daily application of tacrolimus 0.03% and CsA 0.05% in treating DED revealed that both medications were effective in controlling signs and symptoms. However, there were no significant differences in efficacy between the two treatments over a 6-month period [177].

Lifitegrast

Lifitegrast (Xiidra®) is an ophthalmic solution approved for the treatment of DED as an anti-inflammatory medication in a concentration of 5% [180]. Lifitegrast possesses anti-inflammatory properties through inhibiting T cell adhesion and migration [181]. It works by binding to lymphocyte function-associated antigen-1 (LFA-1), which inhibits its interaction with overexpressed intercellular adhesion molecule-1 (ICAM-1) on vascular endothelial cells of the inflamed ocular surface in DED [182]. Lifitegrast has been utilized in the treatment of DED across a broad range of severity (from mild to severe) and various pathophysiologic types (ranging from aqueous deficient to evaporative and combined type) [183]. In the trial conducted for the approval of lifitegrast, which involved 771 patients, the use of 5.0% lifitegrast twice daily for 84 days was found to be more effective than the placebo in improving both objective and subjective parameters of DED [180]. In the SONATA study, a multicenter trial involving 331 patients, it was found that the administration of lifitegrast ophthalmic solution at a concentration of 5.0% twice daily for 365 days was effective, well-tolerated, and safe for treating DED [184]. A recent meta-analysis, which included 5 clinical trials, found that lifitegrast was more effective than the placebo in improving OSDI score, ocular surface staining, and TBUT [183]. When administered twice a day, lifitegrast has been observed to improve the signs and symptoms of DED within 2 weeks [180]. The most common adverse effects associated with the use of lifitegrast are instillation site burning, reduced visual acuity, and dysgeusia (a change in the sense of taste) [183, 184].

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are commonly used in general medicine and ophthalmology because they do not require treatment-dependency, unlike steroid therapy, and have fewer adverse reactions. They exert anti-inflammatory effects by inhibiting cyclooxygenase, suppressing prostaglandin synthesis, and downregulating the migration and activity of phagocytes [185]. Pranoprofen drops, which belong to the propionic acid-derived NSAIDs, have been associated with rapid relief of DED symptoms and the stimulation of tear secretion, whether used alone or in combination with

HA. [186] Combining diclofenac eye drops with HA-containing lubricants has also been reported to improve DED symptoms without significant concerns regarding ocular surface irritation or secondary infection after long-term use.[187, 188]. Bromfenac sodium eye drops, as another NSAID, have been shown to be superior to other NSAIDs in terms of penetrability and sustained ocular surface concentration. This allows for long-term inflammation control with fewer daily instillations [189]. In addition to its anti-inflammatory effects on the ocular surface, bromfenac sodium eye drops have also been suggested to enhance lacrimal gland function, which may contribute to its efficacy in treating DED [190]. A recent trial demonstrated that the combination of 0.05% CsA and 0.1% diclofenac sodium eye drops was effective in rapidly alleviating symptoms and improving clinical outcomes in patients with DED [191].

The use of NSAIDs to treat DED may present some challenges. In cases where DED results from immune-mediated diseases such as Sjogren's syndrome, the anti-inflammatory effects of NSAIDs are generally considered inadequate for controlling inflammation of the ocular surface compared to steroid drops [192]. Additionally, certain NSAIDs have been linked to corneal epithelial cell apoptosis and decreased corneal sensitivity in both DED patients and individuals without the condition, which may prompt ophthalmologists to exercise caution when considering NSAID use in individuals with DED [193]. In summary, studies suggest that NSAIDs can effectively alleviate symptoms of mild to moderate chronic DED. However, they should be combined with appropriate tear replacement therapy, monitored carefully, and stopped immediately if there are any new corneal epithelial defects [194]. Patients with common mild DED caused by environmental factors, such as low humidity, are not recommended to be treated with NSAIDs [195].

Essential fatty acids

An elevated omega-3 to omega-6 ratio has been suggested to possess anti-inflammatory properties as arachidonic acid, a component of omega-6 fatty acids, serves as a precursor for various inflammatory cytokines implicated in DED [196]. Omega-3 supplementation for treating DED mainly functions by replacing omega-6 with omega-3, which has anti-inflammatory properties [12]. A 2014 meta-analysis of 5 studies found that increased intake of omega-3 was effective in managing signs and symptoms of DED [197]. A 2019 meta-analysis of 34 trials confirmed the efficacy of long-chain omega-3 supplementation in the management of DED [198]. The dosage of omega-3 supplementation is different based on the formulation and ingredients of the commercial medications. Despite the fact that the efficacy of omega-3 supplementation in reducing DED signs, as measured by the Schirmer test and tear film osmolarity, has been established, there remains uncertainty about its effectiveness in reducing DED symptoms [198]. A trial did not find any clinically significant improvement in DED symptoms after omega-3 supplementation [199].

A recent study showed that a topical formulation containing omega-3 was effective in improving signs and symptoms of evaporative DED over an 8-week treatment period and did not result in significant adverse effects [200].

Mucin secretagogues and mimickers

Diquafosol tetrasodium (DQS)

DQS solution 3% (Diquas®) is a purinergic P2Y2 agonist which increases both mucin and tear production through its effect on conjunctival goblet cells and epithelium [28]. DQS activates intracellular calcium-related cascades after binding to P2Y2 receptors on conjunctival epithelial cells, resulting in mucin secretion and tear fluid production without the involvement of lacrimal gland function [201].

DQS 3% has been shown in numerous studies to improve both signs and symptoms of various types of DED, such as aqueous deficient and evaporative DED [202, 203]. A randomized clinical trial conducted on 286 Japanese patients showed that DQS 1% and 3% ophthalmic solutions administered 6 times per day for 6 weeks were both safe and effective in treating DED patients [204]. During another experiment that compared DQS 3% and HA 0.1%, it was found that DQS was more effective at enhancing Rose Bengal corneal staining. However, both treatments showed similar improvement in fluorescein staining scores [205]. The efficacy of DQS ophthalmic solution has also been reported in contact lens-related DED and dry eye after ocular surgeries [206, 207]. Conjunctival edema

and stinging sensation are the most common side effects of the treatment with DQS [208].

One significant obstacle in the treatment with DQS is the need for frequent administration to achieve the desired therapeutic effect. According to a survey, 80% of patients used DQS 3% four times or less per day, whereas the recommended dosage for optimal efficacy is six times daily [209]. To enhance patient compliance, DE-089C has been proposed as a sustained-release formulation of DQS solution, which requires less frequent administration (three times a day) while maintaining comparable efficacy and safety to the original solution [210].

Rebamipide

Rebacer® and Eyesec®, which contain rebamipide, are other treatments that are based on mucin. They work by stimulating the production of goblet cells and promoting the secretion of mucin, in addition to possessing some anti-inflammatory properties [28]. Rebamipide is an amino acid analog which activates enzymatic production of mucins in different epithelial cells [211]. In conjunctival and corneal cells, rebamipide is believed to enhance the production of both free secreted and membrane-associated mucins [212]. Additionally, rebamipide can decrease the production of inflammatory cytokines, resulting in lower lymphocyte activation and eosinophil infiltration in chronic and allergic inflammation, respectively [213].

The use of rebamipide 2% ophthalmic solution, four times a day for four weeks, has resulted in the stabilization of the tear film and alleviation of both the symptoms and signs of DED [214, 215]. While rebamipide 1% is also an effective treatment for DED, rebamipide 2% may provide better results in certain measures of treatment response [216]. It is well-tolerated and no serious adverse effects have been reported for rebamipide 2% [217].

Vitamin A

Vitamin A in topical forms such as retinyl or retinol palmitate, along with its metabolite retinoic acid, has been proposed as a mucin secretagogue for the treatment of DED. These formulations are available as ointments (0.01%, 0.05%, and 0.1%), gels (0.1%), emulsions (0.01%), and solutions (0.05%) [218, 219]. The parameters that have shown the most significant improvement following topical vitamin A therapy are blurred vision, ocular surface staining, goblet cell density, and TBUT [220]. Based on current literature, topical vitamin A supplementation is typically reserved for patients with severe DED that is unresponsive to other treatments, particularly in those with mucin impairment indicated by clinical tests [221]. In a study that compared the effectiveness of topical vitamin A and CsA in treating severe DED patients, topical vitamin A showed better outcomes in terms of treatment adherence, improvement of blurred vision, and increased Schirmer test scores [218].

Topical vitamin A may have a unique application in future, particularly for the increasing number of glaucoma patients who develop secondary mucin-related DED. A recent study on glaucoma patients with drug-induced damage to their goblet cells found that the long-term use of topical vitamin A was more effective than carbomer gel in increasing goblet cell density and reducing symptoms [222]. It is worth noting that vitamin A can also help reduce epithelial keratinization in cases of ocular surface failure resulting from severe DED or other ocular surface diseases, not just limited to DED [223].

There is evidence to suggest that systemic vitamin A supplementation, whether administered orally or intramuscularly, can lead to improved goblet cell density and repopulation, as well as re-epithelialization of the ocular surface [220]. While the precise role of systemic vitamin A therapy in DED is not fully understood based on current literature, it may be advisable to consider systemic supplementation in patients with confirmed vitamin A deficiency or those at high risk due to inadequate intake.

Lubricin

Lubricin (Proteoglycan 4) is a large glycoprotein primarily produced in synoviocytes to safeguard articular cartilage, and it has also been suggested as a substitute for mucin in the treatment of DED [28]. Lubricin has also been discovered to exist at the normal ocular surface, where it acts as a lubricant for the cornea and conjunctiva [224]. According to a study, recombinant human lubricin was found to be more effective than HA eye drops in providing relief from signs and symptoms of moderate DED [61].

Conclusion

DED is a complex disease that affects the LFU, and recent research has uncovered new aspects of its pathophysiology and potential therapeutic targets. While conventional DED management focuses on breaking the vicious cycle of tear film hyperosmolarity through empirical tear substitution and anti-inflammatory therapy, a more comprehensive approach may be needed. This approach would involve a thorough examination of etiological triggers and adopting a layer-by-layer approach to identify the most impaired component of the tear film. By understanding the classification of DED, using a targeted diagnostic approach for the primary defect, and implementing pathophysiology-specific therapy, the management of persistent DED may be improved. The most recent literature suggests selecting a therapeutic option based on the most affected layer (lipid versus aqueous versus mucin) and determining the intensity of treatment based on the severity of the condition.

Literature search

For this review article, an extensive literature search was conducted on electronic databases, such as PubMed, Scopus, and Web of Science. The search was limited to human studies published in any language up to March 2023. The search was conducted using the following keywords: "dry eye syndrome," "ocular surface disease," "medical management," "artificial tears," "topical immunomodulators," and "meibomian gland dysfunction." In addition to the electronic database search, the reference lists of relevant articles were also reviewed to identify additional studies. The inclusion criteria for this review article were studies investigating the medical management of dry eye syndrome, including randomized controlled trials, systematic reviews, and meta-analyses.

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Declarations

Conflict of interest The authors declare no competing interests.

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