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REVIEW

Personalized Management of Dry Eye Disease: Beyond Artificial Tears

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Abstract: Dry eye disease (DED) is a multifactorial disease of the ocular surface that may be accompanied by discomfort and visual disturbances to a level that reduces quality of life. Artificial tears are a common first-line therapy for DED that aim to supplement the tear film but do not address the underlying causes of DED. Because of the complexity and variability of the disease, personalized treatment beyond artificial tears is important for successful management. This review describes artificial tears and the current knowledge in the personalized approach to the management of DED. There is evidence that artificial tears can reduce symptoms and signs of DED; however, a proportion of patients have been found to show limited or no improvement with artificial tears. Furthermore, the effectiveness of artificial tears may depend on patient compliance and type of artificial tear product used. Personalized management of DED with other treatments involves identifying features of the disease, including the subtype of DED, the presence of inflammation, and the coexistence of external and behavioral contributing factors. Various measures exist to characterize DED, including assessments of the tear film lipid layer, the meibomian glands, tear volume, tear osmolarity, and matrix metalloproteinase 9 levels. Because individuals can show variable features, the most prominent clinical findings, comorbidities, triggering events, and treatment history should be considered to determine the best treatment choices for patients.

Keywords: dry eye disease, inflammation, individualized, customized, evaporative, aqueous deficient

Introduction

Dry eye disease (DED) has been defined as a multifactorial disease of the ocular surface characterized by a loss of homeostasis, 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 estimated prevalence of DED varies widely across studies.[2] In a large analysis of claims data, overall prevalence of DED between 2003 and 2015 was estimated to be 5.28% in the United States, and annual incidence between 2008 and 2012 ranged from 0.55% to 0.87%.[3] Risk factors for DED include but are not limited to older age, female gender, certain autoimmune diseases, contact lens use, certain topical and systemic medications, and environmental conditions.[2,4–6] DED may be accompanied by symptoms such as discomfort, pain, and visual disturbance, which may reduce quality of life and interfere with productivity.[2,7,8] Elevated tear film osmolarity and ocular surface inflammation may result in ocular surface damage,[9] while tear film inadequacies may contribute to lid wiper epitheliopathy.[10]

Clinical guidelines have been developed for the diagnosis and management of DED,[11–13] including the reports of the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II).[12,14] Diagnostic testing for DED involves the assessment of symptoms (eg, with the Ocular Surface Disease Index [OSDI], Schirmer test or Standard Patient Evaluation of Eye Dryness Questionnaire) and clinical signs of DED, including reduced tear breakup time (TBUT), increased tear film osmolarity, and ocular surface staining with fluorescein and lissamine green dyes.[14,15] Additional assessments, such as matrix metalloproteinase-9 (MMP-9) testing and eyelid imaging, can further characterize the disease,[16,17] which can be helpful in guiding treatment decisions.

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Artificial tears are a common first-line therapy for DED; however, they are typically not sufficient or effective in managing the disease.[12] Fortunately, a variety of other treatments and procedures are available.[12] Because the features and subtypes of DED vary across patients, it is important that treatment for DED is tailored to individual patients. In the present review, we describe artificial tears and the current knowledge in the personalized approach to the management of DED.

Considerations in the Personalized Management of DED

Personalized management of DED involves considering features of the disease, the patient, and the patient's environment to identify the treatments that best suit the patient.[11,18] Important features to consider include the subtype of DED, the presence of inflammation, and the presence of external and behavioral factors that may be contributing to the DED.

Subtypes of Dry Eye Disease

DED may be categorized into evaporative and aqueous deficient subtypes.[9] Evaporative DED is characterized by an increased rate of tear film evaporation with normal lacrimal function, while aqueous deficient DED is characterized by decreased secretion of tears from the lacrimal glands with a normal rate of tear film evaporation.[7,9] These subtypes are typically overlapping, concurrent, and driven by inflammation.[1,19] Patients may also fit neither subtype, as some patients with DED have symptoms without signs.[14] For example, in a study of 224 individuals with DED, only 159 could be categorized as evaporative, aqueous deficient, or mixed subtype, based on TBUT and the Schirmer score.[20] The evaporative subtype was found to be the most common subtype, with 49.7% of patients having evaporative DED, 14.5% having aqueous deficient DED, and 35.8% having a mixed subtype.[20] Subtypes are helpful in thinking about the mechanism of disease, which may be used to guide treatment decisions.

Evaporative DED may initiate from eyelid-related factors, such as meibomian gland dysfunction (MGD), or may initiate at the ocular surface (eg, from ocular surgeries or medications).[1,9] Normal meibomian gland functioning is important to slow tear film evaporation, as the meibomian glands release lipids that make up the outer layer of the tear film.[11,14,21] Individuals with DED can be assessed for evaporative DED through measures of the tear film lipid layer using interferometry or through various assessments of the meibomian glands, including meibomian gland expressibility and meibomian gland loss (ie, dropout).[14,22,23] Meibomian gland loss has been found to correlate with age, suggesting that changes in meibomian glands should be expected in older individuals.[22,24] Notably, a decreased number of meibomian glands in the lower eyelid yielding liquid secretions has been found to correlate with greater dry eye symptoms.[25] Furthermore, among those with MGD, meibomian gland atrophy has been found to correlate with reduced lipid layer thickness.[26]

Aqueous deficient DED may be related to a variety of etiologies and can be subclassified as Sjögren syndrome related or non–Sjögren syndrome related.[9] Sjögren syndrome is an autoimmune disease with lacrimal gland infiltration that can result in aqueous deficient DED.[12,27] However, like the general population of individuals with DED, patients with Sjögren syndrome may show signs of both aqueous deficient and evaporative DED.[9,28] In addition to Sjögren syndrome, lacrimal deficiency may be related to a variety of other diseases, such as graft-vs-host disease, or natural changes observed with aging.[9,29] Corneal neurosensory deficits may also play a role in aqueous deficiency, given that corneal sensation is involved in promoting tear production.[30] This is supported by the finding that individuals with aqueous deficient DED have lower corneal subbasal nerve density than individuals with evaporative DED.[30] Assessment of aqueous deficient DED may be conducted with measures aimed at assessing tear volume, including the Schirmer test and measures of tear meniscus height.[14] As might be expected, Schirmer I scores (without anesthesia) were found to be lower in individuals with Sjögren-related DED than in individuals with DED without Sjögren syndrome.[31] Furthermore, individuals with aqueous deficient DED based on low Schirmer I scores (≤ 5mm) and TBUTs (≤5 seconds) were also found to have smaller tear film thickness and tear meniscus height than normal controls, consistent with the concept that low Schirmer scores are indicative of tear film aqueous deficiency.[32]

Inflammation in Dry Eye Disease

Ocular surface inflammation has been identified as a core feature of DED that can occur with both aqueous deficient and evaporative DED.[9] Tear hyperosmolarity in DED is thought to initiate a cycle of inflammation, tear film instability, and further tear hyperosmolarity.[9,33,34] Therefore, addressing inflammation may be an important component of the management of DED. Individuals with DED have shown signs of inflammation in the form of increased inflammatory cell density in the corneal epithelium, increased HLA-DR expression in the conjunctival epithelium, and increased cytokine expression in tears.[33,35–39] Elevated levels of inflammatory markers in DED have been found both in individuals with and without immunologic disease.[35–37] However, those with immunologic disease have shown higher levels of inflammatory markers than those without immunologic disease.[35–37] Severity of MGD has also been associated with levels of inflammatory markers, in that levels of cytokines (IL-17A and IL-6) in tears showed moderate to strong correlations with meibomian gland secretion scores in those with DED because of MGD.[40]

Assessment of inflammation in DED has been conducted through impression cytology, in vivo confocal microscopy, and collection of tear samples.[35–37,39–41] In addition to these methods, a point-of-care test may be used to detect elevated levels of MMP-9 in tears.[16,42] MMP-9 is an enzyme that plays a role in extracellular matrix remodeling.[16] Increased MMP-9 levels have been considered a marker of inflammation in DED,[42–44] as increased MMP-9 levels have been observed in conjunction with increased cytokine levels in dry eye models.[45,46] Higher rates of elevated MMP-9 levels (≥40 ng/mL) have been found in individuals with DED compared with normal controls.[16,47] For example, among 47 individuals with various levels of DED severity, 40.4% were found to have a positive MMP-9 test compared with 5.6% of controls.[16] Ocular surface signs (ie, corneal staining scores and TBUT) have been found to be worse in those with positive MMP-9 tests than in those with negative MMP-9 tests among those with DED.[44] Furthermore, MMP-9 expression has been found to correlate with ocular surface staining in individuals with Sjögren syndrome and in individuals with MGD.[48] In individuals with Sjögren syndrome, MGD, or thyroid orbitopathy-related DED, use of topical anti-inflammatory therapy has been associated with a reduction in MMP-9 levels.[48–50]

External and Behavioral Factors

Several external factors have been linked to DED, including use of contact lenses and certain ocular medications.[6,51–54] Identification of these factors, specifically the patient's medical and ocular history, is important because it allows for modifications that may improve the patient's DED. For example, use of topical antiglaucoma medications has been associated with DED,[52,53,55,56] which may be caused by preservatives such as benzalkonium chloride.[57,58] Therefore, switching to a preservative-free antiglaucoma medication may help improve DED. Furthermore, the patient's environment may change from day to day, which could be addressed by customizing artificial tear instillation frequency.

Behavioral factors that may contribute to DED include insufficient or incomplete blinking and poor compliance to prescribed therapeutic regimens. Insufficient blinking allows for high levels of tear evaporation, which may initiate the cycle of DED.[9] Patients can be observed for frequency and completeness of blinking while they are in the clinic.[14] Patients can also be asked about their digital screen use patterns since screen time has been associated with both DED and insufficient blinking.[59–65] In addition to reduced blinking, poor treatment compliance may limit the benefits of treatment for DED.[23] With therapy consisting of artificial tears, patients have been found to use fewer drops per day than recommended and to commonly report depletion of medication as the reason for discontinuation.[66] Identification of these behavioral factors is beneficial because they suggest the need for additional patient education. Furthermore, poor treatment compliance may suggest the need for additional and/or alternative therapies to address the DED.

Artificial Tears for Dry Eye Disease

Artificial tears are a therapy for DED that aims to supplement the tear film.[11,12,67,68] They have been found to improve symptoms and certain signs of DED but are not thought to address underlying causes.[12,23] A wide variety of artificial tear formulations are available to address DED.[12]

Properties of Artificial Tears

Artificial tear formulations differ in properties such as viscosity, osmolarity, and presence of substances such as osmoprotectants, lipids, and preservatives.[1,12,69–71] Artificial tears with higher viscosity, such as ointments and gels, are intended to have higher ocular-surface retention time but may result in blurring of vision.[72] The viscosity of certain artificial tears is designed to decrease during the blink cycle (a property known as shear thinning), which, in turn, has been postulated to minimize visual blur.[68] Osmoprotectants, such as L-carnitine, may be included in artificial tears to help protect cells against higher tear osmolarity.[12,70,71] Lipids may also be included to supplement the lipid layer of the tear film.[73] In addition, artificial tears may include preservatives, disappearing preservatives, or may be preservative-free.[4] Preservative-free artificial tears eliminate the risk of ocular surface changes associated with preservatives.[12,74] Although a wide variety of artificial-tear formulations is available as treatment options for DED, this broad array may also make it challenging for patients and clinicians to identify the best artificial-tear product for the patient.[75]

Efficacy of Artificial Tears

Artificial tears have been found to reduce symptoms and signs of DED.[76,77] For example, in a study of 394 patients with DED, treatment with artificial tears (containing either carboxymethylcellulose [CMC] and hyaluronic acid or CMC without hyaluronic acid) resulted in an approximately 16-point improvement in OSDI score at day 90 (scale: 0–100).[77] Improvements were also observed in TBUT, ocular surface staining, and Schirmer scores (with anesthesia).[77] In a separate study of 99 patients with DED, 69.5% showed a treatment response at day 30, defined as an improvement of ≥4.5 points in OSDI score and/or an improvement of >4 seconds in noninvasive TBUT. By day 180, the rate of treatment response increased to 74.2%.[23] Improvements in tear film lipid quality were observed but only for patients who received lipid-based artificial tears, suggesting that lipid-based artificial tears may be helpful for patients with tear film lipid layer deficiencies.[23] Overall, these studies show improvements in DED with artificial tear use. Notably, however, approximately 26% of patients did not show a response to artificial tears in the latter study.[23] In fact, non-responder OSDI scores and noninvasive TBUTs worsened by 2.4 points and 0.5 seconds, respectively.[23] These findings demonstrate that certain patients with DED may show limited or no response to treatment with artificial tears.

Compliance with Artificial Tears

The efficacy of artificial tears for DED may depend on the consistency and frequency of their use by patients. In a 6-week study comparing outcomes in patients who were randomized to artificial tears 4 times per day (QID) or artificial tears as needed, patients in the QID group showed greater improvement in the Impact of Dry Eye on Everyday Life symptom bother score than patients in the as-needed group.[72] Real-world evidence suggests that patients with DED use fewer eye drops per day than recommended and often use eye drops on an as-needed basis.[78] These findings suggest that real-world outcomes with artificial tears may not reflect outcomes demonstrated in clinical trials in which patients showed high adherence to artificial-tear regimens. In a clinical trial by Craig et al,[23] a longer time course was needed for improvements in ocular signs of DED compared with symptoms, suggesting that clinical improvements in DED with artificial tears may only come with prolonged compliance.

Treatments for Dry Eye Disease: Beyond Artificial Tears

The major cause of DED for each patient should be identified and therapies should be based on individual characteristics. Depending on the severity and subtype, the presence of inflammation, and the presence of external and behavioral factors that may be contributing to DED, the management of DED may be different between individuals and even different during various stages of a patient's life. The goal of management is to restore homeostasis of the ocular surface. Indeed, the TFOS DEWS II Management and Therapy Report highlights that for DED, a step-wise treatment approach is not possible due to the complexity of the disease and the variability between patients.[12] Furthermore, management of DED may require more than one treatment and thus patient understanding of the benefits and limitations of their treatments, as well as their expectation needs to be discussed. Behavioral changes should be encouraged, for example healthier digital screen habits.[59] For inflammation in DED, several topical anti-inflammatory therapies exist, including corticosteroids, cyclosporine, and

lifitegrast.[50,79–85] These therapies have been recommended as potential treatment options for both evaporative and aqueous deficient DED.[11] For patients with MGD, additional treatment options include warm compresses with lid massage, manual meibomian gland expression, oral omega supplements, thermal pulsation, intraductal probing, intense pulsed light, and topical antibiotics, which are aimed at improving meibomian gland expressibility.[22,86–92] For patients with aqueous deficiency, additional possible therapies include moisture chamber eye wear and punctal plugs, which are aimed at improving retention of the aqueous tear film.[93,94] Importantly, eyelid disease and inflammation may need to be treated before the insertion of punctal plugs so that infection and inflammatory mediators may first be cleared.[12] Therapies to promote tear production include varenicline solution nasal spray, external neurostimulation, and oral pilocarpine.[95–97]

Patients with DED may show a mixture of clinical features, including inflammation, MGD, and aqueous deficiency. Therefore, the most prominent clinical feature may need to be considered at the start. In addition to comorbidities, possible triggering events (eg, prior surgery, medications, and contact lens use) are factored in to identify disease characteristics and shape treatment decisions. History of previous treatments can provide guidelines for new or supplemental therapies. Notably, patients may show changes in disease characteristics over time, which may require corresponding adjustments in treatment.

Follow-up after initiating various treatments is highly recommended to confirm patients are adhering to treatments as well as ensuring improvements are occurring to the ocular surface.

Conclusions

The etiology of DED is multifactorial, and thus management of DED cannot be considered as a one-size-fits-all. Personalized treatment for DED involves clinical assessments of tear film and meibomian gland function, as well as taking the patient's medical and treatment history into consideration. The TFOS DEWS II Management and Therapy Report reports various treatments for DED, including topical prescriptions (corticosteroids, secretagogues, antibiotics, LFA-1 antagonist drugs), oral antibiotics, lid hygiene, warm compression, therapeutic contact lenses, moisture chamber and even surgical punctal occlusion.[12] Artificial tears are one of the options in the armamentarium of therapies for DED, and customization of the treatment will likely contribute to the success of DED management because of its complexity and variability among patients.

Abbreviations

CMC, carboxymethylcellulose; IL, interleukin; MGD, meibomian gland dysfunction; MMP-9, matrix metalloproteinase 9; OSDI, Ocular Surface Disease Index; QID, 4 times per day; TBUT, tear breakup time; TFOS DEWS II, Tear Film & Ocular Surface Society Dry Eye Workshop II.

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Laura Periman is an advisor for Allergan, Avellino, NuSight Medical, ScienceBased Health, Sun, ThermaMEDx; consultant for Allergan, Alcon, Bruder, Eyedetec, Eyevance, Horizon, Kala, Mallinkrodt, Novartis, NuSight Medical, Olympic Ophthalmics, Omera, ScienceBased Health, Sun, TearLab, ThermaMEDx, Wellness 26; a speaker for Allergan, Alcon, Eyevance, Johnson & Johnson, Lumenis, Mallinkrodt, Novartis, NuSight Medical, Optase, ScienceBased Health,

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