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Dry eye: why artificial tears are not always the answer

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ABSTRACT

Dry eye disease (DED) is a multifactorial disease that manifests in patients with a variety of symptoms and signs such as ocular pain, visual issues, rapid tear evaporation and/or decreased tear production. It is a global health problem and is the leading cause of optometry and ophthalmology clinic visits. The mainstay therapy for DED is artificial tears (ATs), which mimics tears and improves tear stability and properties. ATs have been found to improve symptoms and signs of disease in all DED subtypes, including aqueous deficient DED and evaporative DED. However, given the heterogeneity of DED, it is not surprising that ATs are not effective in all patients. When AT fails to relieve symptoms and/or signs of DED, it is critical to identify the underlying contributors to disease and escalate therapy appropriately. This includes underlying systemic diseases, meibomian gland dysfunction, anatomical abnormalities and neuropathic dysfunction. Thus, this review will discuss the benefits and limitations of ATs and review conditions when escalation of therapy should be considered in DED.

INTRODUCTION

Dry eye disease (DED) is defined as 'a multifactorial disease of the ocular surface characterised 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 aetiological roles'.[1] The heterogeneity of the disease is apparent within this definition. DED can present with a variety of symptoms (pain or vision related) and signs, such as decreased tear production, rapid tear evaporation and ocular surface inflammation, that are often discordant.[2]

Putting aside the complexity, DED is a growing health problem worldwide, with a global prevalence estimated to be between 5% and 50%, depending on the disease definition and the population examined.[3] In Canada, one-fourth of ophthalmic visit patients reported some level of DED symptoms.[4] The high prevalence of DED translates to a great financial burden on US healthcare systems—estimated at US$3.84 billions.[5] It also translates to a decreased quality of life for patients.[6] For example, utility score analysis equates moderate DED to moderate angina and severe DED to a disabling hip fracture.[7] Unfortunately, the disease is frequently chronic, lasting years, and if not properly treated, vision-related symptoms and the social impact of DED can worsen.[8]

Overall, the disease is more common in women than in men, with menopausal women being at highest risk, and the frequency of disease increases with increasing age.[9 10] Younger individuals, however, can also have DED, which in this group has been associated with the use of digital devices (eg, phones, computers).[3] Other risks for DED include contact lens use, hormone therapy, antihistamines, antidepressants, refractive surgery, diet and smoking.[11 12] The key to remember, however, is that different risk factors are associated with different DED subtypes.

As mentioned above, symptoms of DED are a leading cause of visits to optometry and ophthalmology clinics.[13] DED symptoms can be divided into two categories: dysesthesias/pain and vision related. Dysesthesias associated with DED are most often described as dryness, but can also include burning, aching and tenderness, to name a few.[14] These symptoms can occur spontaneously or be evoked by wind and light. Vision-related DED symptoms can manifest as blurry or fluctuating vision.[14] Interestingly, DED symptoms often do not correlate with clinical signs of disease.[15] Clinical signs of DED are often split into two main categories: aqueous deficient DE (ADDE) and evaporative DE (EDE), both of which can be accompanied by ocular surface inflammation and high or unstable tear osmolarity. More than 80% of cases fall into the EDE or ADDE+EDE categories, while 10% are solely ADDE.[16 17] In addition, underlying systemic diseases like Sjogren's syndrome (SS) and graft-versus-host diseases (GVHDs) are related to DED.[18] Anatomic abnormalities, such as eyelid laxity and conjunctival chalasis, and neuropathic ocular pain also often coexist and may contribute to tear abnormalities.[19–21] Inflammation may play a role in both categories, with inflammatory cytokines,

IL (Interleukin)-1β, TNF (tumor necrosis factor)- α and MMP-9 (matrix metalloproteinase 9), being implicated in disease and the cycle of damage.[17] For example, inflammation can prevent mucin secretion and further cause tear film instability.[11]

Artificial tears (ATs) are the first-line treatment of therapy for DED—no matter the subtype.[16 22] ATs are thought to improve DED symptoms by mimicking tears and improving tear stability and properties (eg, osmolarity).[17] Given the high prevalence of DED, it is no surprise that more than 60 million people worldwide are estimated to use ATs with a market growth rate 12% per year.[23] In fact, Americans spend up to US$320 million on ATs per year.[11] On an individual level, people spend approximately US$126 per year on over the counter treatments for DED—including topical therapy and nutritionally supplements.[5] ATs do have advantages in that they protect the ocular surface and may help reduce ocular surface inflammation.[24 25] However, they do not address all contributors of disease and thus do not alleviate symptoms in all individuals.[26] The goal of this review is to discuss the efficacy of ATs and when escalation past AT need to be considered.

WHAT ATS ARE AVAILABLE FOR USE?

There are many different types of ATs available that contain different types of lubricants, chemical properties and preservatives (figure 1).[11] AT should be tailored to an individual patient, based on tolerability, visual needs and frequency of use.[25] The US Food and Drug Administration (FDA) designates ATs based on their specific active demulcents or emollients.[27 28] Demulcents are water soluble polymers that protect and lubricate mucous membrane surfaces and relieve dryness and irritation. Examples include carboxymethylcellulose (CMC) and propylene glycol. Emollients, such as mineral oil and petrolatum, are fat-based or oil-based products meant to retard tear evaporation.[27 28] Inactive ingredients that are not included in the FDA's monograph are hydroxypropyl (HP) guar, sodium hyaluronate (SH) and castor oil.[27 29] However, it is important to recognise that different regions have different regulatory requirements and that an ingredient listed as active in one region may be considered inactive in another.

Furthermore, ATs have different levels of viscosity. Viscosity increases retention time and thus increases length of hydration. Patients with more advanced DED generally need higher viscosity ATs to control their symptoms.[25] However, high viscosity ATs can blur vision and cause stickiness and eyelash crusting.[30] Preservatives are another important component of ATs. Unlike preservative-free products that only allow for one dose and are costly, preservatives provide antimicrobial activity so that ATs can be used more than once.[31] There are benefits to preservatives, such as financial advantages and increased compliance; however, they can be toxic to the eyes.[31] For example, products with benzalkonium chloride were found to increase corneal epithelial permeability by 3.1 times, while products without the preservatives increased permeability by 1.7 times.[32] Other preservatives are less toxic but still have negative effects on the ocular surface, including cell wall destabilisation and irritation, if used frequently.[31] ATs without preservatives are recommended if used more than 4–6 times a day.[25]

WHEN DO ATS WORK?

Aqueous deficiency

By supplementing patients' tears, ATs can provide the necessary lubrication and stabilise the tear film for patients with ADDE.[27] One study examined the efficacy of three ATs among 60 patients with ADDE: CMC 0.5% (Cellufresh), SH 2.5% (Blink Intensive Tears) and HP guar 0.18% (Systane).[33] ADDE was defined as OSDI (ocular surface disease index) Score between 30 and 60 and Schirmer test <7 mm, and each patient applied their assigned AT four times a day for 30 days. Symptoms were not reassessed at 30 days but all three groups exhibited an improvement in TBUT (tear film break up time) and Schirmer test. Interestingly, there were no significant differences in TBUT and Schirmer scores between the different ATs studied at 30 days. Compared with baseline, ATs were also found to decrease osmolarity at day 30 (CMC: 320.6±2.0→318.0±1.3 mOsm/L; SH: 320.9±3.4→316.8±2.5 mOsm/L; HP guar: 321.9±2.7→317.1±1.6 mOsm/L). This study suggests that various commercially available ATs are equally able to improve ADDE signs.[33] Another study compared different concentrations of SH (0.1%, 0.15% and 0.3%) and topical cyclosporine (CsA) 0.05% on patients with ADDE (TBUT <5 s, Schirmer test <10 mm and fluorescein corneal staining ≥4 points).[34] A total of 176 patients were randomly divided into four groups and were instructed to instil their respective eye drops every day for 12 weeks (five to six drops a day for SH 0.1%, 0.15% and 0.3%; two drops a day for CsA). All four groups demonstrated a statistically significant improvement in OSDI scores from baseline to week 12, but there were no significant differences between the groups (SH 0.1%: −12.4±19.2; SH 0.15%: −11.9±14.5; SH 0.3%: −12.1±18.5; CsA 0.05%: −17.9±20.6). Similarly, TBUT values improved for all groups with no significant difference between the groups at week 12. All groups exhibited an increase in the Schirmer test; however, the SH 0.15% group's Schirmer test performed significantly better at week 12 than the SH 0.1%, SH 0.3% and CsA 0.05%. Lastly, conjunctival staining also improved for all four groups with a greater reduction in staining in the SH 0.1% group at week 12.[34] Thus, ATs, including CMC, varying concentrations of SH and HP guar, may be sufficient in improving symptoms and signs of individuals with ADDE.

ATs are even as effective as prescription products for some aspects of ADDE. For example, one study compared SH with diquafosol ophthalmic solution, a P2Y2 purinergic receptor agonist that stimulates aqueous

and mucous secretion directly on the ocular surface. This medication is available in Japan, but not yet in other countries.[35] In 286 patients with ADDE (Schirmer test≤5 mm, fluorescein and rose bengal staining scores≥3 points), individuals were randomised to diquafosol or SH six times a day for 4 weeks.[36] Dry eye symptom scores (11 symptoms, and each symptom scored 0–3 based on severity) improved significantly more in the diquafosol group compared with SH. TBUT increased significantly in both groups and there was no difference between the two groups at week 4. Similar findings were noted for fluorescein staining score (−2.1±0.1 in the diquafosol group and −2.1±0.1 in the SH group). This study suggests that AT can improve some aspects of ADDE, such as TBUT, or fluorescein staining.[36]

One cause of ADDE is SS, a chronic autoimmune disorder characterised by exocrine gland dysfunction of the lacrimal and parotid glands.[3] A prospective case–control study explored the effects of CMC sodium 0.5% (Refresh Plus) in individuals with SS-associated ADDE (n=17), non-SS-associated ADDE (n=5) and controls (n=33, no symptoms, Schirmer test >20 mm and no corneal fluorescein staining).[37] ADDE was defined as having Schirmer test <10 mm and corneal fluorescein staining in a sicca pattern. Immediately after instillation of AT, an improvement in Surface Asymmetry Index (1.0±1.2→0.6±0.3, p<0.002), potential visual acuity(20/33.5±20/14.0→20/23.0±20/5.7, p<0.001) and astigmatism (2.1±2.0→1.5±1.1, p=0.04) was noted for all individuals with ADDE (SS associated and non-SS associated). Although only examined in the short term, this study indicates that ATs can reduce corneal surface irregularity and improve visual acuity and astigmatism.[37] Another study examined the effects of HP methylcellulose 0.5% (HPMC) in 14 individuals with SS and 10 individuals with non-SS-associated DED (TBUT ≤5 s or Schirmer test ≤5 mm and fluorescein score ≥1 points or rose bengal ≥3 points).[38] Patients were instructed to apply the preservative-free HPMC 0.5% for four times a day for 1 month. By the end of the study, the total subjective scores (14 symptoms, each scored 0–5 based on severity) decreased more robustly in the SS (11.6±2.1 to 6.2±2.8, p<0.001) versus non-SS group (12.2±2.1 to 8.1±2.6, p<0.001). Interestingly, TBUT, fluorescein staining and rose bengal staining improved significantly only in the SS and not in the non-SS group. Although a more robust study is warranted, this suggests that after 1 month, HPMC may improve symptoms and signs in some individuals with SS, even more so than in individuals with non-SS DED.[38] Lastly, SH of different osmolarity (hypotonic hyaluronate 0.4% vs isotonic hyaluronate 0.4%) were compared in 40 individuals with primary and secondary SS-related ADDE (Schirmer test ≤5 mm, fluorescein and rose bengal stains>3 points).[39] ATs were instilled six times a day for 90 days. The total subjective symptom score (six symptoms, each scored 0–3 based on severity) significantly decreased in both groups (hypotonic: 11.7±3.1→1.6±1.2; isotonic: 11.4±1.8→2.1±1.0, p<0.001) to a similar extent at day 90. TBUT and rose bengal conjunctival staining improved in both groups, but the hypotonic group demonstrated a greater improvement in both signs. Overall, this suggests that SH has an overall benefit in individuals with SS, with hypotonic SH being slightly superior to isotonic SH.[39] Thus, even in patients with severe ADDE, as is often seen in SS, ATs can help reduce symptoms, signs and subclinical metrics of disease.

Lipid dysfunction

Greater than 80% of individuals with DED have a component of hyperevaporation which often coexists with meibomian gland dysfunction (MGD).[17] An abnormal lipid layer is thought to underlie this DED subtype. The lipid layer normally reduces aqueous evaporation by 90%–95% and reduces the surface tension of the tear film phase by 25%.[40] Patients without a visible lipid layer have a fourfold higher rate of tear film evaporation than patients with a continuous lipid layer, regardless of thickness.[41] Lipid-containing eye drops have thus been developed to more closely mimic the aqueous and lipid components of the tear film layer.[42] Active ingredients in these ATs that help compensate for the lipid layer include light mineral oil, mineral oil, castor oil, glycerin and polypropylene glycol at varying concentrations (figure 1).[17]

One randomised, masked study compared Systane Balance (a lubricant containing emulsions of oils) to saline in 49 individuals with EDE (symptoms, TBUT ≤7 s and evidence of MGD).[43] Subjects applied their assigned AT four times a day for 4 weeks. Individuals treated with Systane Balance had a greater reduction in corneal and conjunctival staining at 4 weeks compared with saline (−80.0% vs −10.4%, p<0.001) and improved meibomian gland functionality. At 4 weeks, fewer individuals treated with Systane Balance had a meibomian gland expression grade of 2 or 3 compared with the saline group (28% vs 46%).[43] In another study, 75 individuals with EDE (symptoms, TBUT <10 s, thin-film interferometry grades of 1 and 2) were randomly assigned to SH 0.15% (Lubristil), HPMC (Dacriosol) or an oil-in-water emulsion (Emustil).[44] After using the assigned AT four times a day for 90 days, some subjects in all groups had a reduction in the frequency and severity of symptoms (the SANDE (Symptom Assessment questionnaire iN Dry Eye). The frequency of symptoms improved in a similar proportion of individuals in all groups (50% in the SH group, 56% in the HPMC group and 83% in the Emustil group). TBUT on the other hand improved for SH and Emustil but not for HPMC. Fluorescein staining improved only in the Emustil group at day 90. Overall, this suggests that the emulsion AT was superior for multiple aspects of EDE. Similar to patients with ADDE, these data support the notion that individuals with EDE may benefit from ATs.[44]

Potential protective features

Although it is still debated whether ATs are helpful in addressing the underlying causes of DED, studies have highlighted their protective effect on the ocular surface.

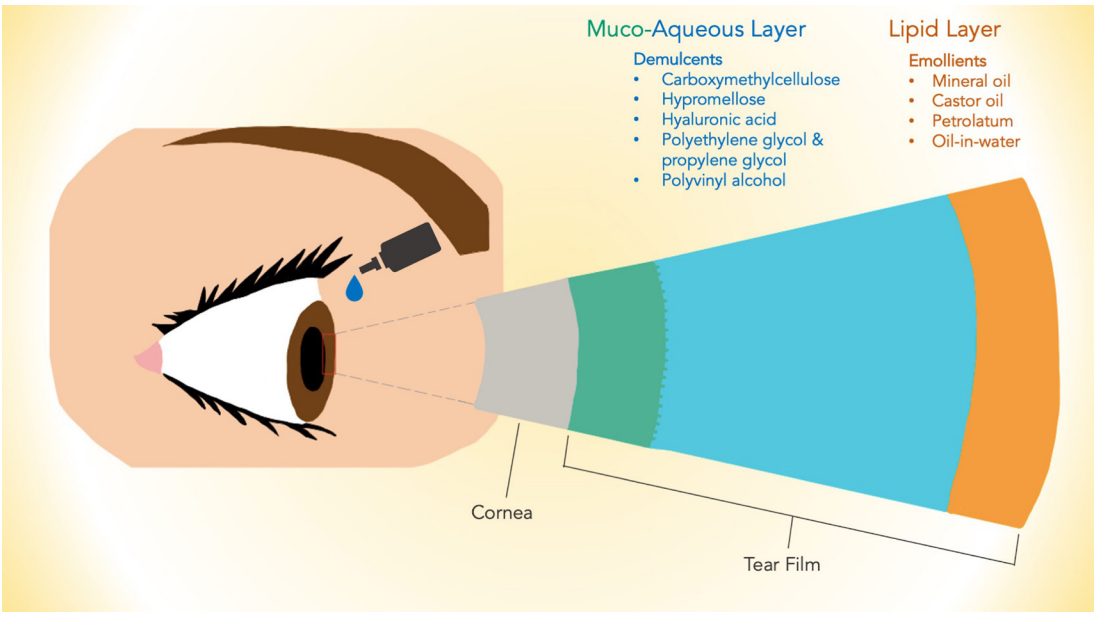

Figure 1 Artificial tears (ATs) and the precorneal tear film. ATs contain compounds that target the tear film at different levels (mucin layer, aqueous layer, lipid layer). Demulcents are water soluble polymers that are used to protect and lubricate the ocular surface. Emollients are fat-based or oil-based products that seek to replicate the lipid layer of the eye, thus preventing the evaporation of the underlying aqueous layer. While ATs have an effective function in targeting abnormalities of the tear film and can also address tear osmolarity and inflammation, ATs may not effectively manage all causes of dry eye (eg, inflammation, anatomical abnormalities, nerve dysfunction) and treatment escalation should be considered in appropriate individuals.

In DED, abnormal tear metrics can increase tear film osmolarity and lead to corneal epithelial cell apoptosis.[17] ATs have been shown to counter this process by decreasing the tear film osmolarity. For example, in the aforementioned study that compared SH, HPMC and Emustil, Emustil slightly improved tear osmolarity from 314 mOsm/L to 311 mOsm/L (p=0.001), whereas no significant changes in osmolarity were noted in the SH and HPMC groups (p>0.05) by day 90.[44] Thus, at least some ATs may impact DED by reducing tear osmolarity, a contributor to DED.[1]

Inflammation also plays a critical role in both subtypes of DED.[1] In a randomised, masked study, 15 subjects with SS-associated or primary DED (symptoms≥2 among soreness, scratchiness, dryness, grittiness, and burning, TBUT <10 s, corneal staining ≥1 points) were given either carmellose sodium 0.5% (Viscofresh) or SH 0.15% (Lubristil) ATs four times a day for 30 days.[45] Subjects treated with carmellose sodium 0.5% AT demonstrated an increase in TBUT from 4.3±1.6 s to 6.6±1.8 s (p<0.00001), whereas there was no significant difference in patients treated with SH 0.15% AT (4.0±1.1 s to 3.9±1.1 s). There were also changes in subclinical signs at day 30 relative to baseline. Both carmellose sodium 0.5% and SH 0.15% ATs decreased the expression of inflammatory marker HLA (human leukocyte antigen)-DR (67.1±18.4→8.9%±9.9%, p<0.0001; 64.2±31.4→36.7%±29.3%, p=0.0006, respectively). In addition, there was a trend toward decreased cellular presence on the conjunctiva measured by the macrophage marker CD11b and the T lymphocytes marker CD3.[45] These data imply that in addition to osmolarity, AT can reduce ocular surface inflammation.

However, not all ATs have an equal effect on ocular surface inflammation. For example, in a superficial keratectomy rat model, the effect of six ATs (phosphate-buffered saline, benzalkonium chloride 0.02% in PBS, Systane Balance, Optive, Vismed and Cationorm) on IL-6 and IL-8 was examined. IL- 6 is an acute-phase proinflammatory cytokine and IL-8 is involved in the recruitment of inflammatory cells.[46] IL-6 and IL-8 secretions were quantified by ELISA. After applying the assigned AT two times per day for 5 days, Cationorm, a preservative-free hypo-osmolar cationic oil-in-water emulsion AT, decreased IL-6 and IL-8 secretion by 59% and 74% (p<0.001), respectively. Systane Balance, a soft-preserved iso-osmolar AT, reduced IL-8 secretion by 40% (p<0.01). No statistically significant reductions in IL-6 and IL-8 were observed for the other ATs, indicating that emollient-based ATs may potentially be better than demulcents in decreasing inflammatory cytokines.[46] These data demonstrate that ATs, via their active products, inactive ingredients or product osmolarity, may impact several facets of DED including osmolarity and inflammation, but that not all ATs are identical in their effects on the ocular surface. These data highlight the need for studies that compare the effects of different ATs on ocular surface inflammation in humans. To summarise, AT may improve facets of DED in various DE subtypes, including both ADDE and EDE. However, not all individuals sufficiently respond to AT. It is thus important to recognise when it is time to move on and escalate treatment beyond AT alone.

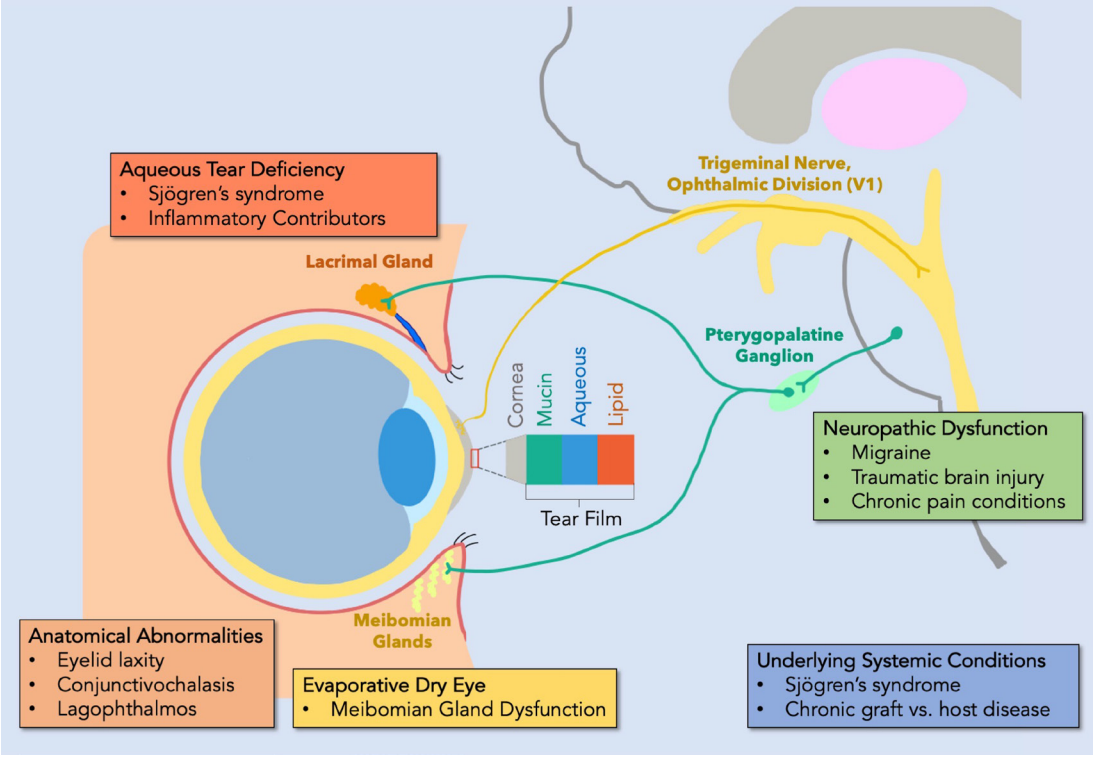

Figure 2 Contributors to dry eye. Dry eye is a heterogenous, multifactorial disease characterised by a combination of ocular surface symptoms and signs that can be attributed to several key contributors. These categories include nociceptive causes, encompassing aqueous tear deficiency (eg, lacrimal gland dysfunction in Sjogren's syndrome (SS)), evaporative dry eye (eg, meibomian gland dysfunction) and anatomical abnormalities (eg, conjunctivochalasis, floppy eyelid syndrome), as well as neuropathic contributors. Neuropathic dysfunction may result in abnormalities in gland function or sensory processing (peripheral or central), particularly in association with migraine, traumatic brain injury and chronic pain conditions (ie, fibromyalgia). Dry eye disease may also occur in the setting of systemic disease, such as SS and graft-versus-host disease.

WHEN SHOULD TREATMENT BE ESCALATED BEYOND ARTIFICIAL TEARS (ATS)?

According to the FDA, ATs are indicated for the 'temporary relief of burning and irritation due to the dryness of the eye'. If ATs do not sufficiently address symptoms and signs of disease, individuals need to consider additional or different treatment modalities.[27] One study surveyed 100 eye care providers and found that 81% used ATs as a first-line therapy for DED. However, 86% of respondents indicated that 20% or more of their patients failed treatment with ATs alone.[47] In this review, we discuss why AT may not be sufficient to treat symptoms and signs of DED in all individuals (figure 2).

Inflammation

Inflammation can be both a cause and result of tear film instability. Increased osmolarity can induce ocular surface inflammation, and the inflammatory cytokines can subsequently lead to a decrease in goblet cells and disrupt the corneal barrier. In order to stop this inflammatory cycle, inflammation must be targeted.[48] As mentioned above, some ATs have been found to decrease ocular surface inflammation; however, some individuals with DED may require stronger anti-inflammatory treatment such as with short-term corticosteroids, tetracyclines, CsA or lifitegrast.

Both corticosteroids and tetracyclines (eg, doxycycline) have been found to decrease inflammatory markers in DED. One study randomly assigned 32 patients with moderate-to-severe ADDE to topical AT alone (Refresh, four times a day), AT (4–8 times a day) plus non-steroidal anti-inflammatory drops (NSAID, Ocufen, four times a day) or AT (4–8 times a day) plus topical corticosteroid drops (fluorometholone, four times a day) for 30 days.[49] The ADDE was defined by the presence of symptoms, Schirmer≤7 mm and corneal punctate fluorescein score of ≥1. After 30 days of treatment, individuals who received AT+steroid had significantly lower symptom severity scores than the other two groups. They also had significantly lower rose bengal staining, whereas there were no significant differences between day 0 and 30 for the AT alone group or AT+NSAID group. Lastly, the AT+steroid group demonstrated a significant decrease in the expression of HLA-DR on conjunctival cells (14→10%, p=0.04), whereas the other groups did not have a significant decrease in HLA-DR expression.[49] These data highlight that corticosteroids reduce ocular surface inflammation to a greater degree than a combination of NSAIDs and AT or AT alone in individuals with ADDE.

Animal models have substantiated findings in humans. Mice were given a subcutaneous injection of scopolamine

hydrobromide to induce ADDE and were then treated with balanced salt solution, preservative-free methylprednisolone 1% (Leiter's) or preservative-free doxycycline 0.025% (Leiter's) four times a day for 5 days.[50] These mice were compared with control wild-type mice and untreated dry eye induced mice. The study found that production and activity of MMP-9 increased after scopolamine injection. However, dry eye induced mice that were then treated with methylprednisolone or doxycycline had significantly lower levels of MMP-9 (0.35±0.07 and 0.54±0.14 relative fold of expression, respectively) compared with untreated dry eye induced mice (~1.5±0.1 relative fold of expression) (p<0.0001). Similar results were seen with other proinflammatory cytokines, including TNF-α, IL-1α and IL-1β transcripts. This mice-model study demonstrated that after 5 days, corticosteroids and tetracyclines can help to decrease MMP-9 and proinflammatory cytokines that are elevated in DED.[50] Corticosteroids, however, have the potential for long-term side effects, and as such should be used in the short term and judiciously in the long term, in individuals with DED.[51]

CsA is another anti-inflammatory agent well studied in DED. Its mechanism of action is to block the translocation of transcription factors that are required for T-cell activation and inflammatory cytokine production.[52] In one study, topical CsA+AT versus AT were compared in individuals with mild-to-moderate ADDE (TBUT <10 s and Schirmer test <10 mm).[53] The study group (n=22) was randomly assigned to CsA 0.05% (Restasis; two times per day for 4 months) and preservative-free AT (HPMC 0.3%/dextran 0.1%, Tears Naturale Free; four times a day for 4 months), whereas the control group received AT (n=20) four times a day for 4 months. Conjunctival lissamine green staining was graded from 0 to 5 according to the Oxford grading scheme. Treatment with topical CsA+AT improved TBUT (~4.2±1.8→7.0±2.0 s), Schirmer test (~4.4±3.0→9.4±2.6 mm) and lissamine conjunctival staining (~2.3±1.0→0.8±0.8) to a greater degree than AT alone (TBUT: 4.4±1.8→5.2±2.8 s, p=0.02; Schirmer test: 4.4±1.8→6.0±3.0 mm, p=0.002; conjunctival staining: ~1.9±0.9→1.6±1.1 points, p=0.02).[53] This study indicates that using combination CsA and AT can improve ocular surface health more long term, beyond AT alone.

Beyond inflammation, normal tears contain anti-inflammatory factors, such as transforming growth factor beta (TGF-β), that are secreted by the lacrimal gland and conjunctival goblet cells.[54] CsA has also been found to increase goblet cell density and TGF-β levels. For example, six individuals with ADDE were treated with AT (Refresh Plus, four times a day for 4 weeks) followed by 0.05% CsA emulsion (Restasis, two times per day for 12 weeks). ADDE was defined as having OSDI Score ≥25, Schirmer test <10 mm, corneal fluorescein staining score ≥3 points and conjunctival lissamine green staining score ≥3 points.[54] After 4 weeks of AT, there was no difference in mean goblet cell density compared with the baseline. However, after 12 weeks of CsA therapy, goblet cell density increased by 2.8 times in the temporal conjunctiva and 3.1 times in the inferior bulbar conjunctiva, relative to treatment with ATs (p<0.01). TGF-β2-positive goblet cells significantly increased after 12 weeks of CsA treatment. Those data indicate that CsA may re-establish balance on the ocular surface, increasing anti-inflammatory and decreased proinflammatory mediators in eyes with ADDE.[54]

Lifitegrast is another anti-inflammatory molecule studied in DED. Lifitegrast is an integrin antagonist that inhibits T-cell adhesion, migration, activation and subsequent cytokine release.[55] In a 12-week study, 718 individuals with ADDE (visual analogue score ≥40, Schirmer test ≥1 and ≤10 mm, corneal fluorescein staining ≥2 points and conjunctiva redness score ≥1 points) were randomised to lifitegrast (n=358) or placebo (n=360) (two times per day for 84 days). After 84 days of treatment, eye dryness scores (−35.3±28.4 vs −22.75±28.6) and eye discomfort score, as determined by the visual analogue score (−0.9±1.3 vs −0.6±1.4), decreased more significantly in the lifitegrast versus placebo group. The corneal fluorescein staining scores also decreased more significantly in the lifitegrast than the placebo group (−1.6±2.0 vs −1.5±2.1, p<0.0001).[55] Thus, patients with ADDE may find relief with lifitegrast.

What is missing in the literature is a comparison between anti-inflammatory therapies in individuals with ADDE. As such, it is not possible to predict which anti-inflammatory agents (eg, CsA vs lifitegrast) are optimal for a particular individual. Nevertheless, these data indicate that additional anti-inflammatory treatments may be necessary for patients who are no longer responding well to ATs.

Underlying systemic diseases

DED can occur in the setting of systemic diseases, such as SS and GVHD. For example, in a single centre, 24 of 220 (10.9%) individuals with DED had a diagnosis of primary SS.[56] Eight individuals had the diagnosis at time of presentation, 12 were diagnosed during the initial evaluation and four were diagnosed during follow-up through a salivary gland biopsy.[56] As mentioned above, conventional ATs may help patients with SS-related ADDE. However, given the central role of inflammation in SS, it is not surprising that anti-inflammatory agents are often needed in individuals with SS-associated DED. One randomised study assigned 30 patients with DED in the setting of secondary SS to topical CsA 2% (n=15) or olive oil (n=15) for four times a day for 2 months.[57] Mild discomfort was observed in 3 of the 30 eyes receiving CsA and 2 of the 30 eyes receiving olive oil. TBUT significantly improved in the topical ciclosporin 2% group compared with the placebo group (CsA: 6.2±0.9→8.5±1.0 s; placebo: 5.8±0.7→5.7±0.8 s, p<0.01) as did corneal staining (CsA: 5.1±0.5→3.4±0.4 points; placebo: 5.4±0.7→5.2±0.6 points, p<0.01). As such, CsA may contribute to improving the ocular health and structural integrity of the corneal epithelium in SS-related ADDE.[57]

Beyond anti-inflammatory agents, other local interventions and systemic medications have also been studied in individuals with SS-associated DED. For example, punctal plugs have been used in this population. One study placed SmartPlug in 22 individuals with primary SS-associated ADDE (Schirmer test <5 mm) and followed individuals for 12 months.[58] Compared with baseline measurements, significant improvements in TBUT (4.6±3.8→7.5±2.5 s, p<0.001) and Schirmer test (2.0±2.7→6.4±5.1 mm, p=0.006) were noted at the 12-month follow-up. This study suggests that punctal plugs may be a simple and effective treatment option for individuals with primary SS-related ADDE. However, the decision to proceed with punctal plugs needs to be made with caution. Punctal plugs may especially be contraindicated in patients with DED due to inflammatory causes and they may cause nasolacrimal drainage system infections.[59] Oral pilocarpine, a cholinergic parasympathomimetic agonist that binds to M3 receptors, has also been studied in relation to SS-associated DED. In one study, 85 individuals with primary SS-associated DED were randomised to pilocarpine (5 mg two times per day) (n=29), AT (n=28) or inferior puncta occlusion (Collagen Plugs) (n=28) for 12 weeks.[60] Individuals who received pilocarpine also had greater subjective improvement (90% improved) compared with AT (30% improved, p<0.001) and puncta occlusion (60% improved, p<0.05), as evaluated by the visual analogue score. While Schirmer scores were similar between the groups, pilocarpine improved rose bengal staining (−1.1±1.0 points, p<0.05) to a greater degree than AT (0.0±0.7 points, not significant) and puncta occlusion (−0.5±0.9 points, p<0.05).[60] Oral pilocarpine, however, has side effects which include nausea, vomiting and sweating that limits its utility in the clinical arena. Overall, individuals with for SS-related DED often need more advanced treatments, beyond AT, to target the various aspects of their disease, namely, inflammation and ADDE.

GVHD is another condition closely linked to DED. Overall, 40%–60% of individuals who undergo a bone marrow transplant develop GVHD with DED usually diagnosed ~6 months after transplantation (median time 171±59 days).[61] Similar to SS, inflammation is a core mechanism in GVHD and anti-inflammatory agents are often needed in GVHD-associated DED. One studied examined topical CsA 0.05% (Restasis) in eight patients with GVHD-associated DED who failed to achieve adequate symptom relief from ATs.[62] During the first 3 months, individuals only used AT (at least four times a day) without a significant change in TBUT or Schirmer test (TBUT: 3.4→3.7 s, p=0.2; Schirmer test: 7.1→6.8 mm, p=0.1). Individuals were then treated with CsA 0.05% every 12 hours for 3 months. Of the 16 eyes, there were improvements of tearing in 9 eyes and of burning and blurring in 13 eyes. TBUT also improved from 3.4 s to 6.6 s (p=0.002) and Schirmer test improved from 7.2 mm to 11.3 mm (p=0.003).[62] Although a more robust randomised study comparing AT versus CsA is necessary, many individuals with GVHD-related DED need escalation to CsA if they do not achieve symptomatic relief from ATs alone.

Blood products have also been studied in the treatment of individuals with SS and GVHD. Various methods can be used to prepare blood products for use as topical therapy. For autologous serum tears (AST), after the whole blood is centrifuged, the serum is isolated and diluted to a certain concentration with a sterile saline solution.[63] For platelet-rich plasma (PRP), whole blood is extracted into sterile tubes containing sodium citrate which acts as an anticoagulant. The blood is then centrifuged to separate the plasma fraction from red and white blood cells. Additionally, the plasma fraction can be divided into platelet-rich and platelet-poor fractions, although both fractions are frequently combined. Furthermore, the platelets can be activated with calcium chloride or thrombin to enable the release of their content (growth factors and cytokines), which has been shown to enhance cell proliferation.[64] Blood-derived products are more similar to human tears in their biomechanical and biochemical properties compared with AT.[65] Their components are thought to have biologic effects on corneal nerves and promote proliferation and migration of corneal epithelium. They have also been shown to increase goblet cell density and inhibit the release of inflammatory cytokines.[65] In one study, 12 individuals with primary SS-associated ADDE (symptoms, TBUT <5 s, Schirmer test <5 mm and fluorescein vital staining >3 points) were treated with AST 6–10 times a day for 4 weeks and ATs as needed. After 4 weeks, significant improvements in subjective comfort, evaluated by a face score questionnaire, were noted. While there were no changes in TBUT, improvements in the corneal fluorescein staining (5.6±3.4→2.5±2.6 points, p<0.05) and rose bengal staining (5.3±3.6→1.7±2.5 points, p<0.01) were noted.[66] Similar improvements were noted in patients with GVHD-associated ADDE.[67] Fourteen patients with GVHD-associated ADDE (Schirmer test <10 mm and fluorescein and rose bengal stain ≥3 points) were treated with AST 20–30 drops per eye per day for 4 weeks. Symptom scores, as determined by a subjective assessment of symptoms, decreased from 33.7±12.3 to 23.6±10.6 (p<0.01). TBUT increased from 2.8±1.4 s to 5.8±2.1 s (p<0.05) and fluorescein scores decreased from 5.6±2.0 to 2.2±0.9 points (p<0.005) after 4 weeks of AST use.[67] Moreover, there are advantages of activated PRP (also known as plasma rich in growth factors) over AST, including richer concentrations of growth factors and anti-inflammatory cytokines.[64 68 69] While there are no randomised studies comparing PRP to AST in DED, some studies have shown that activated PRP can improve symptoms and signs of DE in individuals who did not respond to conventional treatments (unpreserved AT, punctal plugs, lid hygiene, systemic tetracycline and/or topical corticosteroid).[70] Another study comparing the two blood-derived products in a cell culture model of ocular GVHD found that 20% PRP was significantly more effective than 20% AST

in decreasing the inflammatory markers ICAM (intercellular adhesion molecule)-1 and COX (cycloxygenase)-2 in fibroblastic cells.[71] These data suggest that individuals with systemic comorbidities, such as SS and GVHD, often benefit from escalation of therapy beyond AT.

Meibomian gland dysfunction

MGD is an important cause of EDE and can be improved by ATs. However, some cases of MGD require therapy beyond AT.[72] Antibiotics have been a mainstay therapy in MGD, such as doxycycline and azithromycin. Doxycycline is a tetracycline analogue that has antimicrobial, anti-inflammatory and antimetalloproteinase properties, while azithromycin, a macrolide, inhibits proinflammatory cytokines and is potent against gram-negative microorganisms.[73] Interestingly, azithromycin has also been found to stimulate the accumulation of free cholesterol, neutral lipids and lysosomes in human meibomian gland epithelial cells.[74] In one study, 150 individuals with chronic MGD (meibomian orifice obstruction grade ≥2) whose symptoms were recalcitrant to ATs were randomised to doxycycline 200 mg, doxycycline 20 mg or placebo two times per day for 1 month.[75] There was a slight reduction in number of symptoms in both treatment groups, but not in the placebo group. After 1 month, the number of symptoms decreased from 2.3±1.0 to 1.5±0.6 ($p<0.05$) in the 200 mg doxycycline group and 2.9±0.8 to 1.5±0.5 ($p<0.05$) in the 20 mg doxycycline group. The placebo group changed from 2.1±1.1 to 2.0±1.2 ($p=0.6$). Similarly, TBUT improved in both doxycycline groups (200 mg: 7.8±2.1→9.4±2.9 s, $p<0.05$; 20 mg: 7.8±2.2→9.5±1.6 s, $p<0.05$) but not in the placebo group (7.8±2.1→7.8±2.0 s, $p=0.9$).[75] This suggests the advantages of doxycycline in reducing EDE signs and symptoms for patients with MGD.

Another randomised open label study compared the effects of oral azithromycin with oral doxycycline in MGD.[73] A total of 100 individuals with MGD (symptoms≥2 and signs≥2, with a minimum severity score of 2 for each) refractory to eyelid massages and ATs were included in the study. Subjects were randomly treated with either oral 5-day azithromycin (500 mg on day 1 and then 250 mg/day) or 1-month doxycycline (200 mg/day). Five subjective symptoms and seven objective signs were measured on a 4-point (0–3) categorical scale for a total subjective score of 0–15 and objective score of 0–21. After 60 days of treatment, symptoms and signs in both groups improved, but the azithromycin group had significantly lower ocular surface staining and conjunctival redness compared with the doxycycline group. Overall, the azithromycin group's symptoms decreased from an average score of 7.2±2.3 to 4.3±2.2 ($p=0.001$) and the signs decreased from 10.6±2.7 to 4.8±2.5 ($p=0.001$). The reduction in symptoms and signs in the azithromycin group was more significant compared with the doxycycline group, in which the symptoms improved from 6.8±2.0 to 5.0±2.1 ($p=0.001$) and signs from 11.3±2.2 to 6.7±2.5 ($p=0.001$).[73] A more long-term, randomised study also compared oral azithromycin (1.25 g for 5 days) and doxycycline (4 g for 30 days) for 9 months for patients with MGD and also found that both antibiotics were effective in treating MGD. Similar to the 60-day comparative study, this study also found that individuals assigned with azithromycin had significantly quicker and more maintained improvements during the course than those who were assigned doxycycline. In the azithromycin group, 83% of individuals were stable, meaning that patients had an excellent response and did not require further treatments, versus 34% of the individuals in the doxycycline group.[76] These data suggest that in individuals with MGD who have failed AT, addition of antibiotics is a reasonable next step.

Beyond antibiotics and CsA, various office-based procedures have been evaluated in the treatment of MGD including intense pulse light, thermopulsation treatments (Lipiflow) and meibomian gland probing.[77–79] Each of these approaches are supported by studies that show improvement in symptoms and signs of disease, but more solid randomised control studies or studies that use patients who are resistant to ATs are limited with respect to these newer modalities. However, if ATs are not adequate, some patients with MGD may benefit from treatment escalation, such as antibiotics, anti-inflammatories and office-based procedures.

Anatomical disturbances

Anatomical disturbances of the eyelids, conjunctivae or cornea can lead to DE symptoms and signs that can be recalcitrant to ATs. This includes disorders like conjunctivochalasis (Cch), eyelid laxity and conditions that affect the muscular control of the face (ie, stroke and Bell's palsy) that result in lagophthalmos.[80]

Cch is a common anatomical disturbance that is comorbid to DED. Cch manifests as redundant folds of bulbar conjunctiva that can disrupt tear flow by blocking the inferior nasal punctum and causing decreased tear stability.[19] Lid-parallel-conjunctival folds (LIPCOF) is a metric often used to measure the severity of Cch.[81] The presence and severity of redundant folds have been positively associated with DED symptoms.[19 81] ATs alone have been found to have some benefits in Cch. One study examined the effects of a preservative-free AT called Conheal, containing isotonic glycerol and SH 15%, on 20 patients with severe Cch (lissamine green staining of ≥1 and LIPCOF degree ≥2).[81] After individuals applied both ATs four times a day for 3 months, subjective symptoms based on OSDI decreased from 36.2±25.3 to 15.6±16.7 ($p<0.001$). While the TBUT marginally improved (4.8±1.9→5.9±2.3 s in the right eye, $p=0.02$), the LIPCOF degree decreased notably from 2.9±0.4 in both eyes to 1.4±0.6 on the right eye and 1.4±0.7 on the left eye ($p<0.001$ for both). As such, some patients with Cch-related DED may benefit from using AT.[81]

However, many individuals do not respond to AT and other options, such as surgical removal or shrinkage of the redundant conjunctiva, should be considered.[82] One study examined 15 individuals with grade 3 Cch who

were resistant to various eye drops for at least 8 weeks and underwent the surgery. During those 8 weeks, patients received preservative-free ATs that contained either KCl 0.1% and NaCl 0.4% (Softsantear, 4–10 times a day), fluorometholone 0.1% (Flumetholone, 2–4 times a day) or hyaluronic acid 0.1% (Hyalein mini, 4–6 times a day). After the surgery, a majority of individuals (66.7%) reported symptomatic improvement and TBUT significantly improved (5.7±3.2→8.4±2.5 s, p=0.04). Schirmer values remained stable after surgery.[82] Electrocoagulation of loose conjunctival tissue is a non-surgical option for the treatment of CCh.[83] In one study, 20 individuals with a diagnosis of CCh were treated with electrocoagulation or conventional tear drops including NSAID (ketorolac tromethamine 0.5%, four times a day) and AT (SH 0.15%, six times a day) for 4 weeks. Both groups showed significant improvements in symptoms, but the electrocoagulation group had a greater reduction in OSDI scores (50.7±12.4→19.1±13.9, p<0.001) compared with the NSAID+AT group (50±12→37.7±12.3, p<0.001). TBUT also improved to a greater degree in the electrocoagulation group. Not surprisingly, Cch area decreased in the electrocoagulation group but not in the NSAID+AT group.[83] Thus, restoring conjunctival anatomy is an important component in addressing DED symptoms and signs in individuals with Cch when ATs are not sufficient.

Eyelid laxity, a component of floppy eyelid syndrome, is defined as easily distractible upper and/or lower eyelid margins away from the eye. It is a finding that is often comorbid with obstructive sleep apnea. Patients with eyelid laxity have more abnormal TBUT, Schirmer test, corneal staining, meibum gland drop out, eyelid vascularity and meibum quality than those without the anatomical changes.[20] Interestingly, continuous positive airway pressure (CPAP) therapy, an important treatment of sleep apnea, has also been studied with respect to its effect on DED symptoms and signs. For example, after initiating CPAP, DED symptoms and signs marginally improved in 51 individuals with moderate-to-severe sleep apnea (OSDI: 47.8±21.0→42.2±20.0, p<0.01; TBUT: 7.1±1.8→8.8±1.8 s, p<0.01; Schirmer test 7.2±2.0→8.5±1.8 mm, p<0.01).[84] However, it is important to remember that a poorly fitting CPAP may also be the cause of DED symptoms and signs. While surgical correction of eyelid laxity has also been used to address DED symptoms, data in this regard are limited.[85] Other less invasive approaches, such as taping the eyelids at night or wearing a sleep mask, can minimise night-time exposure in individuals with eyelid laxity.[86]

Neuropathic ocular pain

The ocular surface is populated with nerve fibres.[17 21] Acute injury (eg, surgery) or chronic ocular surface damage may lead to repeated stimulation of peripheral corneal nerve fibres with subsequent permanent changes in both peripheral and central nerves.[87] Patients who have painful DED symptoms may experience unpleasant sensation such as burning, aching and photophobia.[14 88] ATs are often not enough to counteract the pain hypersensitivity that occurs due to reduced activation thresholds of the nerve fibres. In support of this statement, a cross-sectional study examined 118 individuals who reported using AT (Hypromellose 0.4%, Natural Balance) to treat painful DED symptoms.[89] A total of 23 individuals reported no improvement, 73 reported partial improvement and 22 reported complete improvement in ocular pain with AT use. Individuals with no or incomplete symptom improvement with AT had higher eye pain and sensitivity scores than those who had a complete improvement (hot-burning pain: no: 3.0±3.4 vs incomplete: 4.1±3.2 vs complete: 1.8±2.9, p=0.01; sensitivity to wind: 2.4±3.0 vs 3.5±3.5 vs 1.3±2.8, p=0.02).[89] This suggests that individuals with specific DED symptoms (eg, burning, pain with wind and light) are more likely to require treatment escalation past AT than individuals without this symptom profile.

Less data are available on the optimal treatment of painful DED symptoms that occur in the setting of presumed nerve abnormalities. AST, for example, have been evaluated in 16 individuals with presumed peripheral neuropathic ocular pain (complaint of corneal pain≥7/10). In this retrospective, open label study, pain improved from 9.1±0.2 to 3.1±0.3 (out of 10, p<0.0001) after an average of 3.8±0.5 months of AST treatment.[63] Concomitantly, in vivo confocal microscopy found an increase in total nerves (n/frame) and total nerve length.[63] However, limitations in the field include the inability to definitely diagnose the aetiology of pain as peripheral neuropathic and lack of randomised trials evaluating treatment effects.

Topical therapies are likely insufficient in treating individuals with a presumed central component to the ocular pain. Again, while the diagnosis cannot be definitively confirmed with current testing, a central component to pain is suspected in individuals with persistent ocular pain after placement of a topical anaesthetic and in the setting of comorbidities such as fibromyalgia, migraine and traumatic brain injury.[21 90] In these individuals, systemic and adjuvant therapies are often considered. For example, gabapentin, a calcium channel ligand normally used as anticonvulsants, is frequently used to treat neuropathic pain outside the eye.[88] In one study, 72 individuals with presumed neuropathic ocular pain with severe ADDE (painDETECT questionnaire >18, TBUT <5 s and Schirmer test <5 mm) were given either CsA+AT or gabapentin+CsA+AT for 6 weeks. The amount and frequency of treatment were not specified. The OSDI Score improved significantly more in the gabapentin+CsA+AT (66.8±16.1 to 31.1±11.5) than the CsA+AT group (70.1±18.0 to 49.4±16.7) (p<0.0001). TBUT and Schirmer test scores also improved to a greater degree in the gabapentin group after 6 weeks. TBUT increased from 3.7±1.14 to 9.9±1.7 s in CsA+AT group and 3.9±1.3 to 12.8±2.0 s in the gabapentin+CsA+AT group; Schirmer test scores improved from 3.1±1.0 to 10.1±2.6 mm in CsA+AT and 3.8±1.4 to 14.2±3.0 mm in

the gabapentin+CsA+AT group.[91] Lastly, a retrospective study of eight individuals with chronic ocular pain whose symptoms did not improve with AT and other conventional therapies examined the efficacy of gabapentin and pregabalin. Five subjects reported significant or complete relief of ocular pain after either gabapentin (varying from 400 mg once a day or 600–1200 three times a day) or pregabalin (150 mg two times per day) was added to their multimodal treatment regimen.[88] Other therapies that have been used in individuals with presumed neuropathic ocular pain include periocular nerve blocks (4 mL of 0.5% bupivacaine mixed with 1 mL of 80 mg/mL methylprednisolone acetate),[88] botulinum toxin injections[92] and transcutaneous electrical stimulation.[93 94] However, robust studies examining the effect of these modalities in this patient group are lacking and thus an important avenue of future investigations. Overall, in individuals with recalcitrant DED symptoms in the setting of a suspected abnormality in peripheral and/or central nerves, agents that can modulate nerve function should be considered.

CONCLUSION

ATs are the first-line therapy for DED, and they can be beneficial in individuals with both ADDE and EDE. However, ATs are insufficient in relieving symptoms and/or signs in all individuals. When AT fails, alternative therapies should be considered that target underlying contributors to DED. This includes targeting inflammation, underlying systemic diseases, MGD, anatomic disturbances and/or nerve abnormalities. It is essential for providers to identify contributors to DED in an individual patient and consider treatment escalation when ATs are not sufficient. However, the aforementioned studies also highlight limitations in designing treatment algorithms for DED. Specifically, many of the cited studies were limited in size, used different definitions for DED that incorporated several disparate aspects of disease (eg, symptoms, tear stability, tear production) and often reported only within group change. Furthermore, most studies either compared an active drug with placebo or reported outcomes after treatment with one agent. Unfortunately, there are almost no head-to-head comparisons between various DED medication that can shed light on which medications are optimal in a particular patient. These limitations must be recognised, and future studies are needed that can help identify which treatments are most fitting for a specific DED profile.

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