Effective management of dry eye and ocular surface disease

BY ROD MCNEIL

Experts recommend a consistent approach to diagnosis, therapeutic targeting by disease subtype and escalation of therapy when tear substitutes are not sufficient.

Experts call for a consistent, unified approach to diagnosis of dry eye disease (DED), with a new simple diagnostic definition proposed by a global consensus among ophthalmologists, emphasising the importance of tear breakup and subjective symptoms or visual impairment [1]. The definition proposed is: "Dry eye is a multifactorial disease characterised by a persistently unstable and / or deficient tear film causing discomfort and / or visual impairment, accompanied by variable degrees of ocular surface epitheliopathy, inflammation and neurosensory abnormalities."

The purpose is to provide practitioners with a practical tool to allow for a precise and consistent diagnosis of DED in the clinic. The key criteria for the diagnosis of DED are unstable tear film, inflammation, ocular discomfort and visual impairment, and the diagnosis can be made using the DED questionnaire and a slit lamp examination with fluorescein (Figure 1) [1].

Ocular symptoms remain a central feature of DED [2]. Symptom screening with the DEQ-5 or Ocular Surface Disease Index (OSDI) confirms that a patient might have DED, which should then be confirmed through further diagnostic tests (ideally non-invasive) of breakup time, osmolarity and ocular surface staining with fluorescein and lissamine green (observing the cornea, conjunctiva and eyelid margin) [3]. Meibomian gland dysfunction (MGD), lipid thickness / dynamics and tear volume assessment and their severity allow sub-classification of DED as predominantly evaporative or aqueous deficient.

Lifestyle and systemic risk factors for DED

A cross-sectional study in the UK evaluating DED subtypes revealed 38% of general public participants met the diagnostic criteria for DED, 14% with aqueous deficient DED and 30% evaporative DED. Both shared and unique risk factors were identified [4]. Advancing age, female sex, reduced sleep duration, higher psychological stress, and poorer self-perceived health status were independently associated with aqueous deficient DED. Significant risk factors for evaporative DED included advancing age, East and South Asian ethnicity, contact lens wear, increased digital device screen exposure, higher psychological stress and poorer self-perceived health status.

Systemic rheumatologic disease and antidepressant medication were found to be independently associated with aqueous tear deficiency, a New Zealand cross-sectional study showed [5]. Systemic risk factors for MGD included age, East Asian ethnicity, migraine headaches, thyroid disease and oral contraceptive therapy.

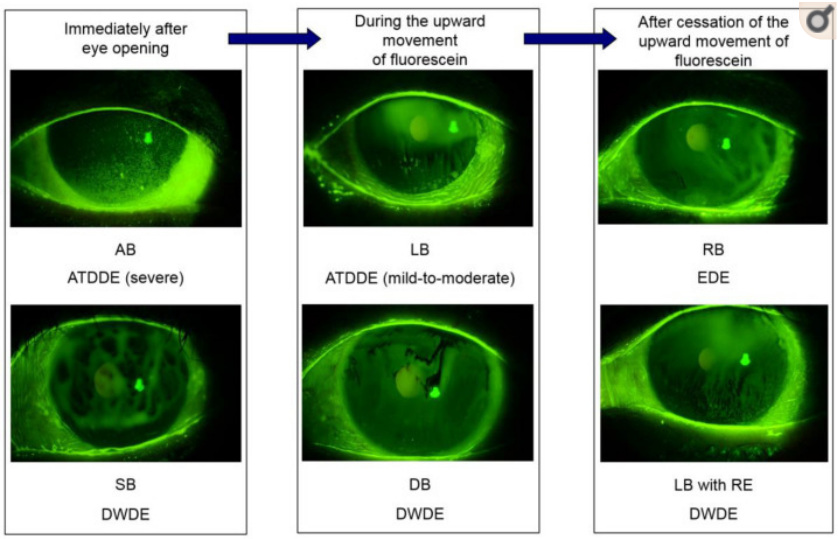

Figure 1: Fluorescein breakup patterns for tear film-oriented diagnosis and their interpretation [1]. Tsubota K, et al. *Int J Mol Sci* 2020;**21(23)**:9271 [1]. Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

Practice patterns in the management of DED

Fewer than half of individuals with dry eye symptoms consult healthcare professionals [6]. Of 916 individuals surveyed in a study of patient-reported experience of dry eye management, about half had tried a treatment for their dry eye symptoms, artificial tears being the most common treatment followed by warm compresses, and both therapies were rated reasonably effective [6].

Among 1,139 eyecare professionals (58% optometrists and 37% ophthalmologists) from 51 countries, general advice (87%), low (85%) and high (80%) viscosity-enhancing unpreserved lubricants and lid wipes / scrubs (81%) were the most commonly recommended management strategies for DED [7]. Treatments prescribed largely independently of severity included artificial tears and nutritional supplements, while oral antibiotics, punctal occlusion, topical anti-inflammatory / immunosuppressants, secretagogues, biologics, therapeutic contact lenses and surgical approaches were prescribed by more practitioners as disease severity increased.

"These international study results demonstrate that practitioners do differentiate treatment strategies according to severity of dry eye disease but that therapeutic targeting by disease subtype is more limited," explained lead author Prof James S Wolffsohn, Optometry and Vision Science Research Group, Aston University, Birmingham, UK, speaking in a telephone interview.

"Widespread use of unpreserved lubricants is reassuring," added Prof Wolffsohn. "The newer-generation artificial tear supplements tend to more closely mimic the composition of the tear film than earlier generation pure viscosity agents. There is also emerging evidence suggesting that artificial tear supplements containing lipids are more beneficial than non-lipid-based agents for individuals with evaporative dry eye disease, by far the commonest form of dry eye disease."

A six-month clinical trial found that, while both lipid and non-lipid-based artificial tear supplements effectively managed most mild-to-moderate forms of aqueous deficient and evaporative dry eye, evaporative cases benefitted preferentially from lipid-based supplementation [8].

Prof Wolffsohn commented: "Another important finding was that those without symptom improvement at day 30 from treatment start failed to benefit from continued therapy out to six months, despite involving a fairly compliant study cohort. If no benefit is seen within a month of starting treatment with a particular artificial tear supplement, it is probably not the most appropriate treatment. We know that the signs follow the symptoms, so it is the early impact of treatment on an individual's symptoms that informs you as to whether there is likely to be a long term impact on their ocular surface."

Ocular lubricants of various types may be considered for managing mild DED, including drops preserved with agents other than benzalkonium chloride (BAK); if MGD is present, lipid-containing artificial tear supplements are recommended [9]. When initial approaches have proved inadequate and for more severe cases of dry eye, non-preserved ocular lubricants should be considered in order to minimise preservative-induced toxicity [9].

When to consider treatment escalation beyond artificial tears alone

While artificial tears can be beneficial as first-line therapy in individuals with either aqueous deficient or evaporative DED, they are not effective in all individuals and escalation of therapy using alternative therapies may need to be considered [10].

Providers need to identify contributors to DED in an individual patient and consider treatment escalation when artificial tears are not sufficient, stressed Kim, et al. [10]. This includes targeting inflammation, underlying systemic diseases such as Sjogren's syndrome and graft-versus-host disease, MGD, anatomic disturbances (e.g. eyelid laxity and conjunctival chalasis) and / or nerve abnormalities (e.g. migraine, traumatic brain injury, chronic pain conditions). Some patients with MGD, for example, may benefit from treatment escalation beyond artificial tears alone, such as antibiotics, anti-inflammatory agents, and office-based procedures such as intense pulsed light (IPL) therapy, thermopulsation treatments and meibomian gland probing.

Repeated short-term pulse therapy of corticosteroids can be beneficial for patients with moderate-to-severe DED not controlled with other therapies [9]. But while patients with worsening dry eye symptoms frequently receive topical steroid courses as needed to improve symptoms, repeated steroids come with additional risks such as raised intraocular pressure, glaucoma, cataracts and increased susceptibility to infections. Topical corticosteroids such as fluorometholone and loteprednol pose a lower risk of corticosteroid-related adverse events [9].

Topical ciclosporin 0.1% (Ikervis, Santen) was approved in 2015 to treat severe keratitis in adult patients with DED that has not improved despite treatment with tear substitutes. A two-year retrospective review conducted at the Tennet Institute of Ophthalmology, Glasgow, found that long-term topical ciclosporin 0.1% treatment was well tolerated and stabilised the ocular surface and symptoms in a cohort of patients with severe dry eyes (n=26) [11]. All patients remained on topical lubricants at least four times daily throughout the study, with rescue steroid therapy avoided in 31% (69% required at least one rescue course of steroids, with almost half of these requiring two or more pulsed courses, to help control symptoms).

Demographics and clinical characteristics at baseline from the European PERSPECTIVE clinical study, recently presented, provide insights into the population likely to attend eye clinics for relief from symptoms of DED and severe keratitis [12]. The reported population was predominantly female (75.8%) and the mean ± SD age was 61.9 ±15.41 years. At baseline, mean corneal fluorescein staining score (Oxford scale grade) was 2.56 and most (81.4%) reported scores below IV. Daily artificial tear use was frequent and insufficient disease control was the main reason for initiating ciclosporin 0.1% eye drop emulsion treatment.

In-office procedures such as IPL therapy and pulsation treatment are often considered for patients refractory to conventional treatment. Treatment applied using the CE-marked Eye-light IPL device (Espasione Marketing S.p.A., Bologna, Italy) consists of four sessions over three months, with each course followed by Low-Level Light Therapy (LLLT) (Figure 2). LacryStim

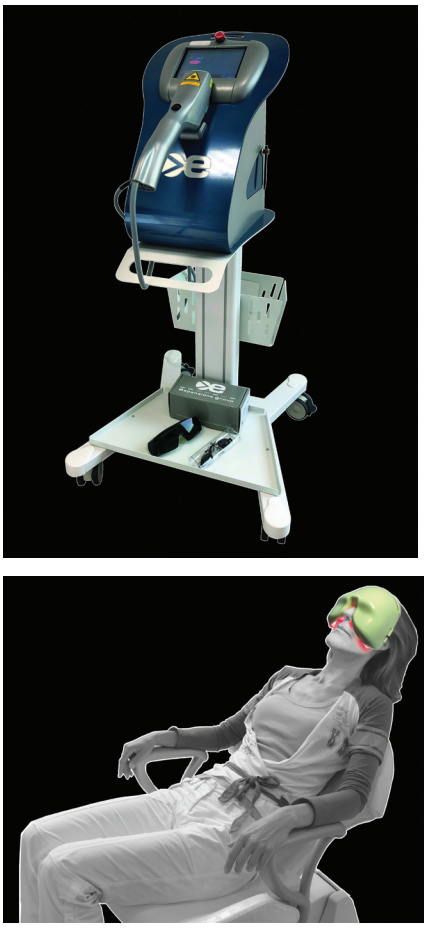

Figure 2: Eye-Light device and LLLT Therapy (courtesy of Espasione).

(Quantel Medical) is an IPL system featuring a unique wavelengths spectrum and train of pulses enabling the stimulation of the lachrymal and meibomian glands and the reduction of inflammation. A long-term muliticentre study showed that Systane iLUX (Alcon) MGD thermal pulsation system is non-inferior to the LipiFlow (J&J Vision) thermal pulsation system in the change from baseline in patient-reported symptoms for up to one year following a single treatment in MGD subjects with evaporative dry eye [13].

Effective treatment options and interventions available to address OSD in glaucoma

Ocular surface disease (OSD) is overrepresented, underdiagnosed and undertreated in glaucoma patients, explained Miss Nishani Amerasinghe, Consultant Ophthalmic Surgeon and Glaucoma Service Lead, University Hospitals Southampton NHS Trust, in a presentation reviewing options for managing OSD and glaucoma during the Glaucoma Subspecialty Day, Royal College of Ophthalmologists 2021 Virtual Annual Congress.

A study of OSD prevalence found that 59% of glaucoma patients reported

symptoms of dry eye in at least one eye and 78% showed abnormal tear quality [14]. Further, each additional BAK-containing eyedrop was associated with an approximately two times higher odds of showing abnormal results on the lissamine green staining test (odds ratio=2.03; 95% confidence interval: 1.06 to 3.89; P=0.034) [14]. Preserved latanoprost eyedrops have been shown to affect ocular surface changes in glaucoma patients through decreased basal tear secretion, with artificial tears providing an early intervention for glaucoma patients with reduced tear secretion and impaired tear-film stability [15].

Effective diagnosis and management of OSD can provide better outcomes for both ocular surface and glaucoma, noted Miss Amerasinghe. Medical approaches include avoidance of preservative-containing glaucoma drops, use of lubricants without preservatives, fixed combination antiglaucoma drops to reduce instillation frequency, topical ciclosporin to improve the ocular surface and potentially consideration of omega-3 fatty acid supplementation to treat DED. A prospective multicentre study involving 1,255 glaucoma patients with dry eye symptoms related to antiglaucoma medication reported significant improvement in all dry eye symptoms after 12 weeks of daily dietary supplementation with omega-3 fatty acids [16]. A recent meta-analysis of available evidence concluded that omega-3 fatty acid supplementation significantly improves dry eye symptoms and signs in patients with DED and may be an effective treatment for DED [17].

Initial treatment with selective laser trabeculoplasty for newly-diagnosed glaucoma offers drop-free IOP control (e.g. 74.2% for at least three years) and minimises any potential toxicity [18]. New investigational sustained delivery antiglaucoma therapies may help decrease the need for antiglaucoma drops over time, thereby reducing the toxic load to the ocular surface (e.g. Allergan's Durysta bimatoprost SR, microdose therapeutics, Glaukos' iDose and Santen's polycaprolactone implant with EP2 receptor agonist DE-117).

Also, minimally invasive glaucoma surgery, especially in the form of angle-based surgery or trabecular meshwork bypass surgery, reduces medication dependence. A prospective cohort three-month study showed that implantation of trabecular micro-bypass stent(s) (iStent or iStent inject, Glaukos) with cataract surgery produced significant improvements in ocular surface health, alongside significant reductions in IOP and medications [19]. In the iStent inject pivotal trial, reduction in medication dependence was associated with improved quality of life vs. cataract surgery alone over 24 months, related to improvements in ocular symptoms and vision related activities [20].

Overall, it was noted that there are effective treatment options and interventions available that may help reduce the medication and preservative burden for glaucoma patients and would enhance surgical outcomes of any future bleb-based surgery if required.

Ophthalmic assessment of a large international cohort of treated and stabilised glaucoma patients (n=793, drawn from the Netherlands, Belgium and the UK) found 42.5% suffered from OSD, conjunctival hyperaemia was observed in 32% and positive conjunctival fluorescein staining in 10.3%. Additionally, patients reported symptoms upon instillation (31.4%) and between instillations (57.3%). All ocular signs and symptoms were significantly ($p<0.001$) associated with patient dissatisfaction. Some 91.5% of study patients were using preserved glaucoma topical medications and 25.1% were using tear substitutes [21]. Evidence suggests switching from preserved to preservative-free prostaglandin analogue therapy can improve ocular surface tolerance while maintaining effective IOP control [22], and may lead to reduced use of tear substitutes [23].

A recently-published review reinforced the burden of DED both prior to and following cataract surgery, confirming that DED can be induced and exacerbated by cataract surgery. Preoperative assessment for pre-existing DED and appropriate prior treatment is recommended. Surgeons are also encouraged to be mindful of the intraoperative effects of cataract surgery on the ocular surface and to take steps to limit these (Table 1) [24].

Clinical treatments for dry eye in phase 2/3 development

Several novel clinical treatments for symptoms and signs of moderate to severe DED are at or close to late-stage development.

Nasal spray OC-01 (varenicline, Oyster Point Pharma, Inc.), a highly selective nicotinic acetylcholine receptors (nAChR) agonist, is being developed as a multidose preservative-free agent for treatment of the signs and symptoms of DED and neurotrophic keratopathy. Results from the phase 3 ONSET-2 clinical trial demonstrate greater improvement in Schirmer's test score with OC-01 compared with placebo, with a gain from baseline of 10 mm or more by day 28 in 47.3% in the 0.6mg/mL group and 49.2% in the 1.2mg/mL group compared with 27.8% in the placebo group [25]. Overall, the most common adverse event associated with the nasal spray was sneezing (82%-84%). Product launch in the United States is expected later this year, if approved by the US Food and Drug Administration (FDA).

Table 1: Steps to reduce the risk of cataract surgery-related DED, based on current published literature [24].

Pre-operative	Intra-operative	Post-operative
Assess for DED Assess for OSD • Treat pre-existing • DEDMGD	Limit incisional damage • 'Micro'-incisional surgery • Consider avoiding AKs with DED/OSD Limit drop exposure • Avoid XS topical anaesthetic application • Single pre-op. drop of Povidine 5% • Care with pre-op NSAIDS in those with DED • PF drops in those with DED/OSD Limit repeated drying/irrigation • Consider coating OS with dispersive OVD ○ All those with DED ○ As a routine • Limit surgical time where possible Limit Phototoxicity • Reduce surgical time/exposure • Microscope illumination ○ Adequate not excessive Limit surgical trauma • Careful insertion of speculum • Care with FLACS suction ring • Avoid epithelial trauma • Opening FLACS incisions • Limit holding eye with forceps	Assess for DED • Avoid XS drop regimens • Consider PF drops • Lubricating drops/ointment • Management of MGD ○ Lid hygiene ○ Tea tree oil ○ Omega III ○ Topical Azithromicin ○ Systemic tetracycline • Topical Cyclosporin • Other anti-inflammatories ○ Lifitegrast • Mucin Secretagogues • Care with NSAIDs ○ Avoid with DED • Punctal Plugs

DED: dry eye disease; MGD: Meibomian Gland Dysfunction; OSD: Ocular surface disease; NSAIDs: Non-steroidal Anti-inflammatory drugs; FLACS: Femtosecond laser-assisted cataract surgery; OVD: Ophthalmic Viscosurgical Device; XS: Excess; PF: Preservative Free; OS: Ocular Surface.

Topical ointment AZR-MD-001 (Azura Ophthalmics) is an ophthalmic keratolytic being developed for the treatment of lid margin diseases and is described as a novel drug candidate to address hyperkeratinisation in MGD. Interim Phase 2a study results evaluating AZR-MD-001 in individuals with MGD demonstrated statistically significant improvements in signs and symptoms of MGD compared with control [26]. Investigator Laura Downie, The University of Melbourne, considered AZR-MD-001 has potential to be the first pharmacotherapy specifically intended for MGD.

Melanocortin agonist PL9643 (Palatin Technologies) is scheduled to enter phase 3 clinical trial development in the second half of 2021, following positive results from a phase 2 study [27]. These showed statistically significant improvements in multiple signs and symptoms in the moderate to severe dry eye patient population after two weeks of dosing (administered three times daily) and at the 12-week visit.

Data suggest that a novel sirolimus formulation could be used to manage ocular surface diseases and potentially reduce long-term corticosteroid use. A randomised phase 2 clinical trial showed improvement in dry eye symptoms and signs after subconjunctival injection of sirolimus-loaded liposomes in comparison with sham group in patients with poorly controlled moderate-severe DED [28].

Investigational agent ECF843 (Novartis) is a recombinant human lubricin (rh-Lubricin) protein in phase 2 clinical trial development, with part 1 of the study designed to assess safety and efficacy versus vehicle in subjects with moderate to severe dry eye disease (ECF843 0.15 or 0.45 mg/mL BID/TID/vehicle). Primary outcome measures are change from baseline in Symptom Assessment In Dry Eye (SANDE) score, and change from baseline in composite corneal fluorescein staining score. Trial readout is expected in the second half of 2021.

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TAKE HOME MESSAGE

- The key criteria for the diagnosis of DED are unstable tear film, inflammation, ocular discomfort and visual impairment, and the diagnosis can be made using the DED questionnaire and a slit lamp examination with fluorescein.
- If no benefit is seen within a month of starting treatment with a particular artificial tear supplement, it is probably not the most appropriate treatment.
- Consider treatment escalation when artificial tears are not sufficient (e.g. antibiotics, anti-inflammatory agents and office-based procedures such as intense pulsed light therapy and thermopulsation treatment).
- Options to reduce OSD in glaucoma patients include preservative-free or BAK-free medication, decreasing the number of eye drops (i.e. by using fixed combinations), treating the ocular surface with unpreserved tear substitutes and performing earlier laser trabeculoplasty or surgery.
- DED is common and can be induced or exacerbated by cataract surgery, reinforcing the need for careful preoperative assessment for pre-existing DED and appropriate postoperative steps to limit the effects of cataract surgery.

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