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Review

Advances, limitations and future perspectives in the diagnosis and management of dry eye in Sjögren's syndrome

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ABSTRACT

Primary Sjögren's syndrome is a complex systemic autoimmune disorder that primarily affects exocrine glands such as the lacrimal glands. Dry eye disease is one of the most prevalent complications of Sjögren's syndrome, affecting most patients. It significantly impairs quality of life and management is often difficult and unsatisfactory, in part due to weak correlation between symptoms and signs and poor recognition of the three main subtypes aqueous-deficient, evaporative and neuropathic dry eye. This review provides an overview of key aspects of dry eye disease, such as its multifactorial aetiology and recent insights into pathophysiology. The uses and pitfalls of commonly-used diagnostic tests for dry eye are reviewed, as well as the increasing number of new imaging technologies and biomarkers to refine diagnosis. There are many current and emerging treatment options for dry eye in Sjögren's syndrome, but high-level evidence of efficacy is mostly lacking, as are evidence-based treatment algorithms. All these aspects make the management of dry eye in Sjögren's syndrome challenging.

Dry eye: a multifactorial disease

Interest and research in dry eye disease (DED) have increased exponentially over recent decades. 20th century publications on DED primarily focused on Sjögren's syndrome (SS) dry eye (DE), and the pathophysiology of lacrimal glands. In the 21st century, however, the focus of DED changed to eye lids and inflammation of the ocular surface. Although SS was described in 1933, DED was not defined as a disorder until 1995 (1, 2). In SS, autoimmune processes mediate destruction of the (salivary and) lacrimal glands. This can lead to severe aqueous deficient dry eye, due to lack of tear production by the lacrimal glands. Community-based studies show DED is very common, with prevalence estimates ranging from 5 to 50%, depending on the population studied and definition of dry eye used (3). Evaporative dry eye is the most common type of dry eye in population-based studies (2, 4). In this type of dry eye tears evaporate too quickly, leading to tear film instability. When tears prematurely break up, the underlying epithelium becomes prone to damage. The main pathophysiological mechanism of evaporative dry eye is dysfunction of the Meibomian glands. These vertically oriented glands, 20 to 40 in every eyelid, produce a tiny layer of oil on top of the tear film that reduces evaporation of the aqueous and help spread the tears over the ocular surface. In addition to the aqueous and oil layer, a third major component of tears are mucins, that are produced by the goblet cells in the conjunctiva. These mucins are part of the muco-aqueous layer of the tears and help stabilise the tear on the ocular surface (5). Although aqueous deficiency is the hallmark of SS DE, Meibomian gland dysfunction (MGD) and higher tear evaporation is also very common in SS patients (6-9). In addition to aqueous deficient and evaporative dry eye, a third type of dry eye has gained increasing attention recently: neuropathic dry eye (1, 10). In this type patients experience symptoms of dry eye because of nerve dysfunction, either from nerves on the ocular surface (cornea or conjunctiva) or more centrally from higher order neurons (11, 12). All three types of dry eye may be involved in patients' symptomatology. Diagnostic tests and management of dry eye in SS are broadly similar to other patients with dry eye: identification of the types of dry eye and its contributing factors determines the management (13).

The key to successful managing dry eye is understanding that it is multifactorial, i.e. many factors can contribute to dry eye symptomatology. In a recent population-based study of almost 80,000 participants, we found 52 disorders to be independently associated with dry eye, including disorders in almost all organ systems, of which autoimmune, gastrointestinal, psychiatric, functional, ophthalmological, dermatological and allergic disorders were most abundant (14). SS carried the highest risk of dry eye of all disorders, but only accounted for a small population attributable risk (~1%), meaning that non-SS dry eye represents the majority of dry eye in the general population. Other clinic-based studies estimated 10% of patients with clinically significant dry eye have underlying SS (15, 16). Other rheumatological and autoimmune disorders that were associated with dry eye in our study were rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, sarcoidosis, psoriasis, lichen planus, Graves' disease and Crohn's disease. In addition, other chronic pain syndromes, such as fibromyalgia, irritable bowel syndrome and osteoarthritis, were highly associated with dry eye (14). Moreover, in a classic twin study we showed a genetic overlap of pain syndromes fibromyalgia, irritable bowel syndrome and chronic pelvic pain with dry eye, indicating an underlying general pain sensitivity determined by genetic factors (17). Also, environmental factors are important in dry eye (18): for example, air conditioning, wind exposure, low humidity, screen use, air pollution and indoor work have all been linked to dry eye (3, 19). Moreover, several medications are associated with dry eye, such as anticholinergics including antihistamines and antispasmodics, antihypertensives such as diuretics and beta blocking agents, isotretinoin and antiandrogen/oestrogen replacement therapy (3, 20). Treatment of dry eye, including SS DE, should therefore not be limited to the ocular surface but also aimed at understanding all underlying causes and treating these wherever possible, including optimisation of environmental factors (13).

Towards uniform diagnostic criteria of dry eye

To achieve a global consensus concerning multiple aspects of DED, in 2007 the first Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS) was initiated. In 2017 its follow-up TFOS DEWS II took place, which was an international collaboration of 150 clinical and basic research dry eye experts. Its report consists of 11 subreports and many of these are among the most-cited papers in Ophthalmology in recent years (21). Dry eye has been defined by TFOS DEWS II 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). As studies on DED over the past decades have used numerous varying definition criteria of dry eye, TFOS DEWS II set up diagnostic criteria for dry eye to make future studies more uniform and comparable (22). In short, to formally have dry eye, either tear break-up time (TBUT), corneal or conjunctival staining, or tear osmolarity needs to be abnormal (all three point to a loss of homeostasis of the tear film) and symptoms of dry eye need to be present. Further diagnostic tests are advised to investigate the type of dry eye, *e.g.* meibomian gland assessment for evaporative dry eye and tear meniscus height in aqueous deficient dry eye. The assessment of neuropathic dry eye is still in its infancy, as it is characterised by few signs, but *in vivo* confocal microscopy of corneal nerves shows promise (23).

The vicious circle of dry eye

Increasingly attention has been drawn to the so-called vicious circle of dry eye in explaining its pathophysiology (4, 24, 25). Tear hyperosmolarity is considered as the hallmark of dry eye. This can lead to a cascade of events in the epithelial cells of the ocular surface, involving inflammatory mediators and proteases such as IL-1, IFN-γ, TNF-α, and MMP9. This in turn can lead to goblet cell loss, apoptotic epithelial cell death and epithelial glycocalyx damage. This can induce punctate epitheliopathy and tear film instability which can result in tear film break-up before the tear film is renewed by another blink. Such break up exacerbates and amplifies tear hyperosmolarity completing the vicious circle of dry eye. In addition, hyperosmolarity itself can also induce non-apoptotic epithelial cell death. This vicious circle can lead to self-perpetuation of DED (4). Every aetiology of dry eye has entry points to this cascading circle of hyperosmolarity and inflammatory events. Breaking this vicious circle is one of the key aspects of treatment (13).

Lack of correlation between symptoms and signs in dry eye

One of the most intriguing aspects of dry eye is the poor correlation between symptoms and signs of dry eye (22), which we also found in a large clinical cohort of SS patients (26). This lack of correlation is more apparent in women compared to men. Of several dry eye tests, only corneal and conjunctival staining scores were somewhat indicative of dry eye symptom severity (26). Moreover, discrepancy between symptoms and objective measures has also been found as a hallmark of SS in general (27). Interestingly, we showed in a study looking at discordance between symptoms and signs in dry eye that SS has more signs relative to symptoms compared to other aetiologies, but still symptoms do not necessarily reflect "objective" dry eye severity signs (28). It is important to consider what end points to use in treatment studies: objective markers or symptomatology or both. It may be that the duration of the disorder helps explain this discordance (*e.g.* by sensitising the pain system), thus, more longitudinal studies in SS DE are warranted.

Markers of loss homeostasis of the tear film

One of the major drawbacks of diagnostic tests of dry eye are their variability and subjectivity in interpretation. Fluorescein TBUT is one of the most commonly performed tests in clinical practice and is highly influenced

by environmental factors (*e.g.* room temperature, air conditioning), equipment, and the operator's concentration. A tiny break-up in the tears can be easily missed. Scoring of staining of punctate epitheliopathy of the cornea and conjunctiva (such as the Ocular Surface Staining (OSS) scale (29) or Oxford scale (30)) showed high reliability among graders in one study (31), but staining scores can fluctuate over a patient's day and these scales are more difficult to apply to atypical staining patterns. Both TBUT and staining scores are easily affected by the amount of fluorescein instilled and the amount of tear volume on the eye that can vary between patients. To standardise the amount of fluorescein being instilled, the use of a micropipette is recommended, but rarely used in practice (22).

Tear osmolarity is a more objective test gaining popularity over the last 10 years. A "chip-on-a-device" is put in the tear meniscus for a few seconds, after which the device is placed in a machine that measures the osmolarity in mOsm/l (32). This test is more objective, but is unfortunately difficult to perform in patients who have limited volume of their tear meniscus, which is common in SS. Also, tear osmolarity at the tear meniscus does not reflect tear hyperosmolarity at the cornea, which is considered the hallmark of dry eye, but there are currently no techniques in which osmolarity is directly measured on the cornea (22). To overcome some of the problems in diagnostics of dry eye, in recent years increasingly machine operated, more objective tests are introduced. Non-invasive TBUT can be measure with a video keratograph, automatically detecting a break-up in tears without the need to instil fluorescein. Computer automated scoring of staining of the ocular surface is another area worthy of future study.

Markers of aqueous deficient dry eye

For diagnostics and treatment efficacy studies of SS, tests of tear volume are particularly important. The Schirmer test, in which a small paper strip is placed in the inferior fornix of the eye, has historically been used the most to assess aqueous deficient dry eye and SS. After 5 minutes, the amount of wetting (mm) of the strip is measured. The Schirmer test can be performed with topical anaesthesia, in which only basal tear rates are measured, and without anaesthesia, in which both basal and reflex tear production is measured. Due to its discomfort, the test is usually not liked by a patient with (severe) dry eye, and tests show relatively high variability, partly affected by reflex tearing because of irritation of the strip. The phenol red thread test has more recently been proposed as an alternative, in which a yellow thin cotton thread soaked with phenol turns red as a consequence of the more alkaline pH of tears. The thread is, like the Schirmer strip, placed in the temporal one third of the lower eyelid, but only for 15 seconds. Reflex tearing is less a problem and variability has been shown to be low, but its poor correlation with other tear volume tests and dry eye symptoms make its role currently still unclear (22). An increasingly more popular non-invasive objective indirect measure of tear volume is the measurement of the tear meniscus height or area. The tear meniscus is the pool of tears at the junction of the bulbar conjunctiva and the margins of the eyelids that supply to the precorneal tear film. Around 80–90% of the tears are located in the tear menisci. Although it is possible to assess this with a slit lamp in clinical practice with or without fluorescein, measurement with spectral domain optical coherence tomography (OCT) or video meniscometry shows better repeatability and is therefore a preferred method (33-35).

Limitations of dry eye tests in clinical practice

In addition to the examples mentioned above, other imaging-based tests that are gaining popularity are thermography of the tear film, meibography to assess meibomian gland morphology, interferometry of the lipid layer, and *in vivo* confocal imaging of the cornea (22). The exact diagnostic role of some of these tests is still unclear. As yet, among all the promising novel techniques, the role of meibography in ocular surface diagnostics seems to be best documented (36). Meibography allows for the exact assessment of loss of meibomian glands. Hence, patients with substantial loss of meibomian glands can be informed that time-consuming eye-lid hygiene and warming devices are very unlikely to improve their outcome. Thus, morphological analyses of meibomian glands is an important step towards personalised dry eye therapy.

The inflammatory response in SS patients has been shown to correlate to reduced tear production, less stable tear film, and greater ocular surface damage (37). The only method, however, currently available to visualise inflammatory cells directly is *in vivo* confocal microscopy. As these images are readily available at the time of the consultation, they may be used to guide the clinician in prescribing anti-inflammatory therapy.

The primary challenge is that most ophthalmologists or eye care settings neither have special dry eye instruments available nor available time to perform the tests. Therefore, most ophthalmologists are practically limited to using fluorescein TBUT, staining of the ocular surface with fluorescein and/or lissamine green (38), and a Schirmer test, although this is highly variable across different geographical locations. Another limitation is that some of these tests can influence results of other tests, *e.g.* the Schirmer test can cause both staining of the ocular surface and affect TBUT. TBUT can also be affected by Meibomian gland assessment. Clearly, more research is required in this area, including determination of relevant endpoints of treatment studies in SS DE (*e.g.* relevant questionnaires, markers of loss of homeostasis of the ocular surface, tear volume, and inflammation). Specifically, the role of OCT tear meniscus height measurement as an objective measure of tear volume in SS is an area worthy of investigation, as most ophthalmology practices have an OCT available nowadays.

Promising upcoming diagnostic modalities

Vast efforts have been made in recent years in improving the diagnostics and gaining new insights into the

pathogenesis of SS, DED and SS DE (39). Biochemical analysis of tears is a rapidly emerging field, particularly the tear lipidome, mucins, and the proteome, albeit in small studies with few samples and little independent replication. Various mucins have been found to be altered in dry eye, but results between studies are often conflicting. Most consistent among these studies is a decreased MUC5AC expression and altered mucin glycosylation (5). A recent study found tear levels of goblet-cell specific MUC5AC combined with IL-8 as a potential biomarker for differing SS DED from non-SS DED (15). The tear film proteome consists of thousands of proteins, as detected by mass spectrometry in several studies, and is an interesting pool of potential biomarkers for dry eye including SS DE. However, candidate biomarkers in studies so far have usually not been validated by immunological techniques and validation in replication studies is often missing. Another limitation of most of these studies in addition to the limited sample sizes is the preselection of certain biomarkers and the lack of correction for multiple testing. Of interest, a recent hypothesis-free proteomic study found upregulation of pro-inflammatory pathways and proteins involved in ubiquitination (LMo7 and HUWEE1) and B cell differentiation (TTPD52) in the tear fluid of SS patients, while in non-SS DE subjects this was not found. Overexpression of proteins regulating cellular innate and adaptive immunological pathways in extracellular vesicles from tear fluids of SS patients was also found (40, 41). Studies on the tear metabolome have been very scarce but this is an interesting new field with techniques rapidly evolving (42). In a hypothesis-free serum metabolomic study in almost 3000 females, we found low serum androgen metabolites to be highly associated with increased dry eye (43). Androgen deficiency has been linked to lacrimal gland inflammation and MGD, also in SS patients (44, 45). In particular, studies on lipidomics in DED are warranted considering the striking scarcity of such studies in the literature. The key role lipids play in preventing evaporation of the tear film is well established. More recently, certain lipids have been recognised to have anti-inflammatory properties and induce goblet cell secretion (46), adding to the importance of this field. Collectively, clinical studies focusing on lipids in the tear film hold great promise of future improvement of dry eye therapy.

A challenge in -omics studies of tears is to collect sufficient tear volume to perform analyses, especially in SS patients. Salivary gland studies are therefore much more abundant. Nevertheless, this area has a clear potential to aid in the diagnosis, classification and early detection of SS, particularly because techniques are improving and increasingly lower tear volumes are sufficient to do analyses. Recently, a tear proteomics study using flush tears found a more diverse tear proteome and lower spectral intensities of lipocalin-1, lacritin, and prolactin-inducible proteins in SS-DE compared to non-SS DE (47). In addition to tear analyses, developing techniques in imaging, particularly MRI of the lacrimal gland, could also play a role in the diagnosis and early detection of SS, *e.g.* by measuring inflammation and glandular size (48, 50). Similarly, ultrasound of the lacrimal gland might be an area worth of more study in SS (51). To assess neuropathic dry eye, other diagnostic tests such as corneal esthesiometry, pain relief after topical anaesthesia (to test peripheral pain *versus* central sensitisation), and *in vivo* confocal microscopy to assess the corneal subbase plexus nerve density, tortuosity, reflectivity, beading, and presence of neuromas may become more common.

Assessment of symptoms of dry eye

Last but not least, symptomatology is an important, if not the most important, aspect of dry eye. Studies have shown that symptoms of ocular dryness play a major role in the reduction of quality of life in SS patients (52). Numerous questionnaires have been developed to assess symptoms of dry eye. TFOS DEWS II recommends the use of the Ocular Surface Disease Index (OSDI) or the Dry Eye Questionnaire 5 to assess dry eye symptoms (22). The OSDI is a 12-item validated questionnaire including questions about ocular symptoms, vison-related function and problems with environmental triggers, leading to a score of 0 to 100 (53). The OSDI has also been recommended by the European League Against Rheumatism (EULAR), with a cut-off of >33 for severe dry eye (54). The DEQ-5 is a 5-item questionnaire that only takes 2 minutes to complete and assesses frequency and severity of dryness, irritation and watering symptoms of the eyes. A score higher than 6 is regarded as positive for dry eye, and a score higher than 12 is suggested as a cut-off to initiate testing to rule out SS DED (55). We believe the use of more specific symptom questionnaires in SS trials could help better assess patient quality of life. Currently, as an example, the EULAR SS Patient Reported Index (ESSPRI), often used to assess patient's symptoms in clinical trials of SS, only includes 1 question about general dryness of the whole body (56), making it hard to draw specific conclusions about the impact and efficacy on dry eye of new therapies. Finally, to assess neuropathic dry eye, specific pain questionnaires are needed (11).

Diagnostic tools to discriminate SS dry eye from non-SS dry eye

There is a lack of evidence-based tools to determine which dry eye patients should be screened for SS. Early diagnosis of SS is important, to anticipate ocular and systemic complications including lymphoma and cardiovascular events, and for patients' understanding and compliance. A combination of OSDI, TBUT and corneal fluorescein staining has been proposed to discriminate SS patients from dry eye patients with other aetiologies (57). Other studies found conjunctival staining to be a good predictor of SS in dry eye patients (58, 59), but no test or combination have been found to be very sensitive. Other factors that can help discriminate are age and severity, as SS DE patients are generally younger with more severe dry eye (29, 60). In a yet to be published study in our dry eye cohort and from the RESULT (Registry of Sjögren UMCG-Longitudinal) cohort in

the University Medical Center Groningen (UMCG), with approximately 500 Sjögren patients and 500 patients with dry eye from other causes, we found type of symptoms and severity of symptoms non-informative to discriminate between SS and non-SS dry eye. Scoring at least 3 out of 5 abnormal dry eye signs, including abnormal corneal and conjunctival staining, TBUT, presence of mucus, and Schirmer test showed the best accuracy of discriminating SS DE from non-SS DE (AUC of 0.73). Future tear and other ocular surface biomarkers might help in discriminating SS patients from other dry eye patients. As an example, Versura *et al*. showed that several tear protein concentrations (lactoferrin, lipocalin-1, lysozyme-C, albumin) separated SS from non-SS much better than any of the traditional ocular tests mentioned above (61). A recent cross-sectional study looking at three novel serological autoantibodies (anti-salivary gland protein 1 (SP1), anti-carbonic anhydrase 6 (CA6) and anti-parotid secretory protein (PSP)) in aqueous deficient dry eye patients found anti-CA6 to be significantly associated with corneal and conjunctival staining. In addition, anti-PSP was found significantly more often in SS than in other forms of aqueous deficient dry eye. The exact value of these autoantibodies needs to be explored further in larger and longitudinal studies. Because dry eye is highly multifactorial, and numerous other dry eye aetiologies may share pathophysiological mechanisms with SS DE (including the vicious circle), this area of research will probably remain challenging with careful patient selection a key to success.

General management of dry eye

The aetiology of signs and symptoms of DED is multifactorial and therefore clinicians should thoroughly identify the presence of all contributing types of dry eye and other contributing factors, also in the setting of aqueous deficiency in SS. A step-wise approach to the management of dry eye is advised, starting with the more conventional, cheaper and less invasive options (13). The ultimate aim in management is to restore the homeostasis of the ocular surface by breaking the vicious circle of dry eye, and offering long-term option to prevent a return to this cycle (13). Important management strategies in any patient with dry eye include the use of preservative free artificial tears and education about environmental risk factors, such as screen use, contact lenses and air-condition. Standard treatment for evaporative dry eye (MGD), also common in SS patients, includes eyelid hygiene and warming. Although artificial tears are widely used all over the world and numerous types of tears exist, very few studies have compared different artificial tears to assess superiority (62). Artificial tears almost all consist of an aqueous base, but may differ in osmolarity, viscosity and pH, and their viscosity enhancing agents, such as carbomer 940, hyaluronic acid and hydroxypropyl methylcellulose (HPMC). Formulations with additional additives are available, such as lipid supplementations that mimic the meibum oil, or trehalose, an osmoprotectant. It widely varies throughout the world which tears are available and reimbursed, and often a trial and error period is needed in which several artificial tears are used before a patient is sufficiently content. Future studies investigating personalised treatment algorithms by means of artificial intelligence in dry eye are valuable. Artificial intelligence has already proved most useful in diagnostics of retinal diseases (63), however, its use in dry eye diagnostics, is yet to be explored.

EULAR made recommendations for the management of SS last year, based on expert opinion mostly, and advised to start with artificial tears and ointments in case of dry eye, at least twice a day, and if needed up to hourly, preferably containing methylcellulose or hyaluronate. In case of severe dry eye and no good response to artificial tears a stepwise approach of topical glucocorticoids short term, topical ciclosporin long term, serum eye drops and finally oral muscarinic agonist or punctual plugs are advised. In contrast, hydroxychloroquine, systemic immunosuppressive agents, and rituximab were not recommended for the treatment of ocular dryness (54). This recommendation reflects that the value of systemic treatment options for dry eye in SS is unproven at the current time. Several factors may play a role in showing a relatively limited efficacy of systemic treatments in SS DE, including the described variability in dry eye tests, inclusion criteria of clinical studies that primarily focus on systemic manifestations of SS, the relative lack of longer-term studies (more than 24 weeks), and clouding of effect due to simultaneous use of eye drops in most of these studies. Also, study endpoints might need to focus more on stabilisation of tear production as an effect (instead of the normal deterioration), as opposed to an increase.

Medications that reduce inflammation in dry eye

Topical medications that reduce inflammation at the ocular surface that are often used in dry eye are glucocorticoids, ciclosporin, and to a lesser extent tacrolimus. Topical glucocorticoids, such as dexamethasone, methylprednisolone and fluorometholone eyedrops, may reduce inflammatory cytokine expression and many studies including several RCTs have shown improvement of ocular surface parameters after short-term use in dry eye patients (13). A major limitation are their side-effects, particularly increased eye pressure, the formation of cataract, and risk of infections, particularly in severe dry eye. Therefore, they are usually only used short-term (2–4 weeks). Ciclosporin is a fungal antimetabolite that inhibits calcium-dependent IL-2 activation of lymphocytes and is commonly used in patients with organ transplants and in autoimmune diseases. Its topical form is available around the world in two concentrations, Restasis (0.05%) and Ikervis (0.1%), and indicated for moderate to severe keratoconjunctivitis sicca. Although topical ciclosporin has shown to improve signs and symptoms compared to placebo in RCTs, most clearly in patients with severe keratitis including SS patients (64), a recent Cochrane review concluded that evidence of its effects on both symptoms and signs is mostly inconsistent among studies (65). It stressed the need for

well-planned, longer term and larger clinical trials. Ciclosporin is also reported to recover reduced goblet cell density in the conjunctiva in DED patients and to have anti-apoptotic effects (66, 67), Drawbacks are discomfort at installation and the relatively long duration before effects are seen (up to 6 months). Tacrolimus, like ciclosporin, blocks T-lymphocyte activity, but has a much higher immunosuppressive potential. It is available in 0.003% eye drops and was found to improve corneal staining scores and Schirmer test in a small RCT after 3 months in SS patients (68). As with ciclosporin, tacrolimus frequently gives a burning sensation after installation. More recently lifitegrast has been introduced. This integrin antagonist prevents lymphocyte function-associated antigen 1 (LFA-1) from binding to intercellular adhesion molecule 1 (ICAM-1), which downregulates T-cell activation and migration. Several clinical trials showed an improvement in dry eye signs (staining) and symptoms for lifitegrast 5% ophthalmic solution and a good safety profile (69-71). No specific trials in SS patients only were performed, but SS patients were included in some of these trials. The advantage of lifitegrast compared to ciclosporin is its quicker time of action: symptoms improved with lifitegrast in only 14 days. Future studies should evaluate any superiority of these medications and which dry eye patient groups benefit most to achieve personalised dry eye therapy.

Other management options in aqueous dry eye

In SS DE and other aqueous dry eye, punctal plugs are often considered as a treatment option. These plugs prevent draining of the tears to the nose via the lacrimal puncta on the medial sides of the eyelids. Although often applied, evidence of their efficacy on signs and symptoms of DED is inconclusive (72). Importantly, to avoid accumulation of inflammatory mediators on the ocular surface, punctal plugs should not be used before any ocular surface inflammation has first been treated. Systemic medications that can increase tear production, such as pilocarpine and cevimeline, are not often used in dry eye due to their side-effects (excessive sweating and nausea) and their limited effect on ocular dryness as opposed to oral dryness.

Diquafosol is available in an ophthalmic solution at 3% concentration. It stimulates water and mucin secretion by acting on PY2Y2 receptors on the conjunctival epithelial and goblet cell membrane, and is mainly used in Japan and South Korea for the treatment of dry eye. Several RCTs have demonstrated improvement in signs and symptoms of dry eye, including in SS patients (73-75). In the USA, however, 2% diquafosol tetrasodium failed to get FDA approval because endpoints were not achieved (76). Other drugs that target mucus deficiency in dry eye that are investigated and used around the world are rebamipide, galectin-3, mycophenolate mofetil, and eupatilin. Lacritin is a glycoprotein with prosecretory activities, mostly found in the lacrimal gland. Reduced levels were found in SS patients, and levels correlated well with clinical dry eye signs including signs of corneal neuropathy (77). Topical lacritin has been found to decrease signs of dry eye in mice and clinical trials in humans are currently under way (78).

Scleral lenses rest on the sclera, and create a fluid-filled chamber over the affected cornea, which can be an attractive option for aqueous deficient dry eye. Several subtypes are available, such as semi-scleral lenses, mini sceral lenses and PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem). Mostly retrospective case studies have shown efficacy in treatment refractory or severe dry eye (79-83). Limitations are the lengthy and often difficult fitting process, and the increased risk of keratitis in case of a severe dry cornea. Similarly, simple soft bandage contact lenses may reduce symptoms in some patients as they protect the cornea from external influences and may stabilise the tear film, but infection risk also limits its use (13). Moisture chamber spectacles (*e.g.* Blephasteam) provide an environment with high humidity and heat in which air flow over the ocular surface is minimised. Positive effect on patients with DED has been shown (84), but larger, prospective, randomised studies on the impact of humidity in treating DED and MGD are warranted.

Nasal tear stimulation is a new option that works by stimulating mucosal nerves in the nose (anterior ethmoidal nerve) with electrical currents. This increases natural tear production by means of the nasolacrimal reflex pathway of the lacrimal function unit. Several clinical studies in dry eye patients showed an improvement in Schirmer scores, tear meniscus height, and goblet cell density of the conjunctiva, also compared to placebo sham application (85). Future studies should evaluate the efficacy in SS patients, but preliminary results of a clinical study showed intranasal tear neurostimulation to increase tear production in SS patients compared to baseline (86). Nasal discomfort and nasal bleeds and congestion are among the reported side-effects that may limit its use. In a small study, transcutaneous periorbital electrostimulation stimulating the lacrimal system was found to improve DED, both subjectively and objectively, without any adverse effects (87). So far, there are no studies involving patients with SS. More and larger studies are required to explore the potential of this exciting technology that have hitherto shown great promise in certain retinal diseases (88).

Serum drops, either autologous or allogenic, have many biochemical similarities with human tears including pH, nutrients, and growth factors such as epithelial and nerve growth factor. Autologous serum eye drops have been shown to improve at least some dry eye parameters in mostly short-term studies, but large RCTs, especially long-term, are still needed (89). A limiting factor to its widespread use are the time consuming, expensive production costs and difficulties in regulatory approval. With the increasing shift from autologous to allogenic serum drops part of these problems might be solved in the future. Similar to serum, amniotic membrane has beneficial elements such as growth factors, cytokines and collagens to promote wound healing. Amnion membrane transplantation is one of the last resorts in treatment of severe dry eye in SS (13). More recently, the

use of amniotic membrane extract and umbilical cord serum eye drops have been studied as potential treatment options (90, 91).

Mucolytic acetylcysteine eye drops may play a role in treatment of filamentary keratitis of SS, in which strands of degenerated epithelial cells and mucus (filaments) are attached to the cornea. Good quality studies to demonstrate its efficacy are lacking, limiting their widespread use. Recently, chitosan-n-acetylcysteine (Lacrimera), has been introduced, which is based on a chitosan biopolymeric backbone, with the introduction of N-acetylcysteine (NAC) via nucleophilic substitution. Early studies including a RCT versus normal saline eye drops showed improvements in moderate-to-severe dry eye with a once daily instillation (92-94).

Several other new treatment options are currently in development and/or investigated, of which some might be of special interest to SS patients. Examples are newer formulations of ciclosporin that potentially show improved or faster efficacy. Lubricin is a lubricating, mucin-like glycoprotein that lowers friction between the bulbar ocular surface and eyelids, with additional protective effects on underlying cells. It is found on the ocular surface and in the meibomian glands, but was first identified in synovial fluid, playing an important role in lubrication between joint surfaces. In a two-week double blinded RCT lubricin outperformed sodium hyaluronate in patients with moderate dry eye in both signs and symptoms (95). Finally, thymosin β4 is a G-actin binding protein that promotes epithelial healing and reduces corneal inflammation. A topical formulation of 0.1% (RGN-259) showed better improvement than controls in OSDI symptom scores and corneal staining in a phase II RCT (96). It also outperformed ciclosporin, lifitegrast and diquafosol in mouse models on several dry eye parameters including tear production and ocular surface staining scores (97, 98).

Management of Meibomian gland dysfunction

When eyelid hygiene (including warm compresses and eye lid massage) have been unsuccessful in managing MGD, several other options are available, although efficacy is generally not proven. An example is in-office intense pulsed light (IPL) therapy to the eyelids. The exact mechanisms underlying its effects are complex and poorly understood. IPL is, however, believed to liquefy meibum, eradicates Demodex mites and supresses inflammation. Many studies report that IPL is a safe procedure that is effective for treating MGD (99). There is, however, a great potential for further improvements of the technology as large comparative studies employing different treatment settings are lacking. Meibomian gland probing is an in-office procedure using thin probes that are put into the meibomian gland orifices to promote healthy meibum secretion. Lipiflow is a device that is used in-office that expresses and heats the meibomian glands of the upper and lower eyelids, all at the same time. Other in-office systems that aim at maximising meibum liquefaction and secretion by using various ways of heat and/or massage are the MiBO Thermoflo, iLux and TearCare System. BlephEx is an in-office treatment with a handheld device in which a disposable micro-sponge removes debris from the eyelids and eyelashes. This treatment is an alternative or supplemental to the eye lid hygiene performed at home by patients. Also, systemic and local antibiotics, such as tetracycline and azithromycin, may improve signs and symptoms of blepharitis by their antibacterial and anti-inflammatory effects. Many of these treatment options have reached clinical practice without large, prospective randomised clinical trials, which are highly needed to determine their efficacy.

Challenges in the management of dry eye

In conclusion, as described, there are numerous treatment options available for DED. For most of these treatments clinical studies have shown an improvement compared to baseline, but level 1 studies that show efficacy versus placebo in a double-blinded randomised controlled setting are mostly lacking. Most treatments are therefore not reimbursed throughout the world. Also, personalised medicine is an important area of further study, to better perform targeted medicine and avoid lengthy trial and error of management options in dry eye patients. Often patients need multiple treatment options, especially in more severe dry eye such as with SS, and not uncommonly patients fail to improve at all despite the numerous treatment options available. DED related to SS remains a challenge, in part due to its multifactorial nature, the poor correlation between symptoms and signs, and the multiplicity of treatments which have not been compared in randomised clinical trials. Despite this, knowledge on the pathophysiology of dry eye is increasing exponentially in recent years, and there are a range of new treatments emerging, giving hope that more effective therapeutic options are on the horizon.

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