Ophthalmol Ther (2026) 15:1313–1340
https://doi.org/10.1007/s40123-026-01348-7

SYSTEMATIC REVIEW

Immunomodulation of the Ocular Surface in Severe Dry Eye Disease: Expert-Driven Literature Review on Treatment Strategies with Description of Representative Challenging Cases

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Received: November 21, 2025 / Accepted: February 13, 2026 / Published online: March 13, 2026

ABSTRACT

Introduction: Dry eye disease (DED) is a multifactorial inflammatory disorder characterized by tear-film hyperosmolarity, immune activation, and neurosensory dysfunction, which contribute to sustained ocular surface damage. Severe DED is common in autoimmune diseases, especially Sjögren syndrome (SS) and rheumatoid arthritis (RA), and is often refractory to first-line treatments.

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Methods: Current evidence on anti-inflammatory therapies was summarized by experts, and the management of challenging cases of autoimmune-related DED followed in different tertiary centers was presented.

Results: Short courses of topical corticosteroids rapidly suppress disease flares and improve clinical signs, including breakup time and ocular surface staining. However, careful stewardship is required, as prolonged use may elevate intraocular pressure, induce cataract formation, and increase infectious risk. For long-term control, immunomodulators such as cyclosporine A (CsA), lifitegrast, and tacrolimus attenuate T-cell–mediated inflammation, promote goblet cell recovery, and stabilize the tear film. Newer CsA formulations have further improved bioavailability and tolerability. Five challenging cases including DED associated with SS or RA, refractory keratopathy, and corneal epithelial defect were described. Management included biological tears, lid-based care, and punctal plugs combined with once-daily CsA, leading to re-epithelialization, symptom relief, and visual stabilization. Adjunctive measures included oral doxycycline to improve meibomian gland function and reduce inflammation. Regular follow-up optimized treatment tapering, safety monitoring, and patient adherence. In two cases, urgent surgical intervention (conjunctival flap, amniotic membrane transplantation, and penetrating keratoplasty) was required.

Conclusions: Autoimmune-related DED requires a stepwise treatment regimen for the stabilization of the ocular surface and the prevention of irreversible damage. This approach involves an initial short course of corticosteroids, followed by sustained immunomodulation (with CsA as the cornerstone), and supplemented by adjunctive therapies targeting meibomian glands and ocular surface epithelium. Multidisciplinary coordination and regular monitoring are essential for maintaining long-term ocular surface homeostasis and satisfactory quality of life and visual function.

Keywords: Ocular surface; Dry eye disease; DED; Inflammation; Corticosteroids; Cyclosporine; Sjögren syndrome

Key Summary Points

Severe dry eye disease (DED) associated with autoimmune conditions is primarily an inflammation-driven disorder, in which tear hyperosmolarity and immune activation contribute to a self-perpetuating cycle of ocular surface damage.

Short, carefully monitored courses of topical corticosteroids are effective for rapid control of inflammatory flares; however, they should be used with caution due to the risks of intraocular pressure elevation, cataract formation, and ocular infection.

Sustained immunomodulation (primarily with cyclosporine A [CsA], and lifitegrast or tacrolimus as alternatives) restores tear film homeostasis by attenuating T-cell–mediated inflammation and promoting goblet cell recovery.

Adjunctive therapies targeting evaporative and epithelial components (such as lid hygiene and warming, preservative-free tear substitutes, punctal occlusion, doxycycline for meibomian gland dysfunction, and light- or heat-based instrumental treatments) enhance ocular surface stability and reduce symptoms.

A multidisciplinary, stepwise approach with regular follow-up, combining long-term immunomodulatory therapy (often including CsA) with surgical intervention (when necessary), helps prevent irreversible complications and can improve visual function and quality of life in patients with severe autoimmune-related DED.

INTRODUCTION

Severe Dry Eye Disease as a Multifactorial Inflammatory Condition

Dry eye disease (DED) is a prevalent, multifactorial disorder of the ocular surface system, characterized primarily by tear film instability and altered tear composition, leading to tear hyperosmolarity, chronic inflammation, and neurosensory dysfunction [1, 2]. These pathophysiological changes contribute to a self-perpetuating cycle of tear film disruption and ocular surface damage. In advanced cases, DED can result in persistent ocular discomfort progressing to pain, and severe visual disturbances due to corneal damage [3].

The global prevalence of DED varies significantly, ranging from 5% to 30%, depending on diagnostic criteria, geographic region, and demographic factors [4]. Older adults are disproportionately affected by the condition, with particularly high prevalence among postmenopausal women [5]. The disease burden is further influenced by race (higher prevalence among Asian populations), hormonal changes such as androgen deficiency, and the presence of autoimmune comorbidities [4, 6, 7]. Environmental factors, such as low humidity, wind, and air pollution, as well as lifestyle factors, including prolonged digital screen use and contact lens wearing, also contribute to the onset or exacerbation of DED [8]. Certain medications, such as antihistamines and antidepressants, have been implicated as additional extrinsic risk factors [4]. DED is frequently associated with systemic autoimmune disorders, notably Sjögren syndrome (SS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). These conditions contribute to immune-mediated lacrimal gland dysfunction, exacerbating tear deficiency and ocular surface inflammation [6, 7].

DED has historically been classified into two distinct subtypes: aqueous-deficient dry eye (ADDE), caused by reduced tear production, and evaporative dry eye (EDE), often secondary to meibomian gland dysfunction (MGD) [9, 10]. However, most patients present with overlapping features of both types (mixed DED), and effective diagnosis and treatment require consideration of both tear production and evaporation [9, 11]. Regardless of the underlying cause, the vicious cycle of DED is perpetuated by a common pathway involving tear film hyperosmolarity and epithelial stress. These changes induce an innate immune response, activating resident immune cells and promoting the release of proinflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor-alpha (TNF-α), as well as matrix metalloproteinases (MMPs) [2, 12]. These inflammatory mediators induce apoptosis and damage of conjunctival and corneal epithelial cells, reduce goblet cell density and mucin production, and impair lacrimal gland function, resulting in tear deficiency [2, 10, 12]. Chronic inflammation also affects corneal nerves, leading to neurosensory abnormalities that may persist even when clinical signs are mild or absent, complicating both diagnosis and disease monitoring [13]. Over time, the adaptive immune system becomes involved, particularly through $CD4^+$ T-cell responses, further sustaining inflammation and ocular surface damage [14, 15].

Patients with DED commonly report symptoms such as dryness, burning, gritty or foreign body sensation, photophobia, and fluctuating vision [16, 17]. The severity of these subjective symptoms often does not correlate with objective clinical signs, posing a diagnostic challenge. Common diagnostic exams include tear breakup time (TBUT), Schirmer test, ocular surface staining, and analysis of tear biomarkers [18].

DED significantly impairs quality of life by interfering with routine activities such as reading, driving, and prolonged use of digital devices. Chronic ocular discomfort and visual disturbances are also associated with psychological distress, including anxiety and depression [19, 20]. In the workplace, reduced visual function and persistent ocular discomfort can contribute to decreased productivity and overall performance.

The purpose of the present article was to conduct an expert-driven review of the currently available evidence on treatment strategies for autoimmune-related DED and to further provide original insights derived from experts' clinical experience based on the description of

representative challenging cases. This hybrid approach was aimed at providing a comprehensive overview of existing evidence while offering a practical perspective on its application in everyday clinical practice.

METHODS

The present study is an expert-driven narrative review of the literature focused on treatment strategies for the management of autoimmune DED. Articles identified through PubMed and Scopus searches conducted in August 2025 using terms related to autoimmune-related DED and its treatment (including "dry eye disease," "keratoconjunctivitis sicca," "ocular surface inflammation," "topical corticosteroid," "loteprednol," "fluorometholone," "prednisolone," "dexamethasone," "difluprednate," "cyclosporine," "ciclosporin," "Ikervis," "Restasis," "Cequa," "lifitegrast," "tacrolimus," "meibomian gland dysfunction," "Sjögren," "rheumatoid arthritis," "systemic lupus erythematosus") were reviewed. Systematic reviews, randomized controlled trials, and high-quality observational studies relevant to severe and autoimmune-associated DED were selected. Due to the narrative nature of this review, no meta-analysis was performed, and no attempt to exhaustively capture all eligible studies was made; instead, evidence was organized by therapeutic class and clinical applicability. Additionally, original insights obtained by the description of representative challenging cases of severe autoimmune DED followed in different tertiary referral centers for ocular surface diseases were provided to illustrate the clinical relevance and the impact of immunomodulatory therapy in everyday clinical practice.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Written informed consent to publish the clinical details and any accompanying images was obtained from all patients, and all data have been anonymized to protect patient confidentiality.

RESULTS

Treatment Strategies for Ocular Inflammation in Severe DED

The primary therapeutic goal in DED is to restore ocular surface homeostasis by interrupting the inflammatory cycle and preventing its recurrence [21]. To achieve this task, personalized treatment strategies tailored to the DED subtype and individual clinical presentation are required [22, 23]. Customizing therapy is crucial for effective symptom control and long-term disease management. Conventional first-line treatments include tear substitutes to alleviate symptoms and maintain tear film and ocular surface epithelia integrity. In patients with EDE, lid hygiene and warming can be necessary to improve the status of meibomian glands. In patients with ADDE, additional interventions may include tear stimulants and punctal plugs to maintain existing tears [22, 23]. However, most patients with moderate-to-severe disease do not achieve sustained relief with these measures, highlighting the need for therapies that target the immune and neuroepithelial components of the disease [24].

Corticosteroids

Inflammation is central to the pathogenesis of DED, regardless of the underlying etiology [23]. Consequently, anti-inflammatory treatments have become a critical component of the therapeutic regimen [22]. Among these, topical corticosteroids play a crucial role in the management of DED, particularly in patients who do not respond adequately to first-line treatments or in moderate-to-severe cases during acute exacerbations, as short-term induction before longer-acting immunomodulators [22, 25]. Their primary therapeutic action is the rapid suppression of ocular surface inflammation, which contributes to improved tear film stability and production as well as to symptom relief [22, 26]. Topical corticosteroids are effective in rapidly alleviating ocular surface inflammation and associated symptoms in DED [27–29]. Mechanistically,

corticosteroids broadly suppress inflammatory mediator production and immune cell recruitment at the ocular surface, supporting epithelial recovery and tear film stability [21, 26, 30, 31]. Evidence from both animal and human studies supports their efficacy in reducing tear cytokine levels, preserving corneal epithelial integrity, and restoring tear secretion [32–34]. Corticosteroids have also proven effective as induction therapy prior to initiating longer-acting immunomodulatory agents, such as cyclosporine A (CsA) or lifitegrast, which are characterized by a delayed onset of action [26, 35, 36]. Systemic corticosteroid administration may be indicated in patients with concomitant autoimmune disease(s) [37].

The pharmacologic activity of corticosteroids is influenced by their structural characteristics. Modifications to the steroid molecule can alter both potency and safety profiles (Table 1) [38]. Commonly used agents include loteprednol etabonate (topical ophthalmic suspension/gel, 0.2%, 0.38%, 0.5%, or 1%), fluorometholone (topical ophthalmic suspension/ointment, 0.1% or 0.25%), rimexolone (1%), prednisolone acetate (moderate-potency drug, topical ophthalmic suspension, 1%), dexamethasone (moderate-potency drug; topical ophthalmic solution/suspension, 0.1%), and difluprednate (most potent topical corticosteroid; topical ophthalmic emulsion, 0.05%). Prednisolone acetate has higher corneal penetration than prednisolone phosphate due to greater lipophilicity [39]. Differences in clinical effect reflect intrinsic potency, concentration, formulation vehicle, half-life, and ocular penetration [30, 40–42].

Clinical trials have consistently demonstrated the efficacy of corticosteroids in improving both signs and symptoms of DED, such as TBUT, conjunctival and corneal staining, and ocular hyperemia [26, 55–58]. Loteprednol etabonate 0.5% demonstrated effectiveness in reducing inflammation without significantly elevating intraocular pressure (IOP) [29, 43, 46], while fluorometholone 0.1% outperformed placebo in improving ocular surface health in moderate-to-severe DED [58]. In patients with SS-associated DED, prednisolone 0.1% significantly decreased ocular discomfort and epithelial damage [56]. Loteprednol etabonate 0.25% ophthalmic suspension, formulated using mucus-penetrating particle technology to improve drug delivery to the ocular surface, has been approved by the US Food and Drug Administration (FDA) for the short-term treatment of the signs and symptoms of DED and demonstrates a favorable safety and tolerability profile [29, 59].

Despite their clinical benefits, corticosteroids are associated with significant side effects. Long-term use, particularly at higher doses, can result in complications such as increased IOP, cataract formation, and increased susceptibility to ocular infections [22, 29, 37, 60]. Approximately 33% of individuals are moderate steroid responders, with a further 5% being severe responders, experiencing an IOP increase greater than 15 mmHg after 4 to 6 weeks of topical use [61]. Younger patients appear to be more susceptible to steroid-induced IOP elevation [62, 63]. The risk of cataract formation is thought to arise from corticosteroid-induced alterations in gene transcription within lens epithelial cells [64]. Loteprednol etabonate is an ester corticosteroid lacking the C-20 ketone present in many other ophthalmic steroids, and thus is considered less likely to induce steroid-related cataractogenesis than ketone corticosteroids [38, 65]. Prolonged corticosteroid use may impair local immune function, increasing the risk of infectious keratitis, particularly herpes simplex keratitis [26, 66]. Furthermore, corticosteroids have demonstrated limited efficacy in reducing mature corneal neovascularization [67]. Given these risks, they are generally recommended for short-term use in the management of DED [22, 29, 30, 60].

Treatment strategies for DED often begin with a higher-potency corticosteroid (e.g., prednisolone or difluprednate), followed by tapering or switching to a lower-potency agent (e.g., fluorometholone or loteprednol) as symptoms and signs improve [30]. Alternatively, prolonged use of low-potency corticosteroids may be considered due to their more favorable safety profile [68]. In Europe, low-concentration formulations, such as preservative-free hydrocortisone 0.335%, are commonly used and offer a balanced efficacy-to-safety ratio [69]. Steroid stewardship is essential to minimizing harm and optimizing therapeutic outcomes [70]. Glucocorticoid therapy should be individualized to

Table 1 Commonly used corticosteroids in ophthalmology: formulations, key features, and safety

Corticosteroid	Route/formulation + concentration	Mechanism / Key features	Safety	References
Loteprednol etabonate	Topical ophthalmic suspension/gel for the conjunctival sac; 0.2–1.0%	Derived from prednisolone via structural modification Rapidly converted (by tissue esterases) to inactive metabolites after local activity ("soft steroid") Potent anti-inflammatory effect Reduces anterior chamber inflammation (gel) Provides significant pain relief (gel)	Lower propensity for clinically significant IOP rise vs. many ketone steroids (monitoring still required) Minimal systemic absorption Well tolerated with prolonged use Suitable for sensitive patients	[37, 43–46]
Fluorometholone	Topical ophthalmic suspension (instilled into conjunctival sac)/ointment; 0.1–0.25%	Soft steroid with moderate potency Administered into the conjunctival sac Lower aqueous/anterior chamber penetration than dexamethasone/prednisolone in penetration studies (relatively "poor anterior chamber absorption") Limited systemic absorption	Low risk of IOP elevation Safe for mild/moderate ocular conditions	[47, 48]
Prednisolone acetate	Topical ophthalmic suspension; 1.0%	High clinical anti-inflammatory efficacy Excellent corneal penetration Commonly used for acute anterior segment inflammation	Elevated risk of IOP elevation and cataracts with prolonged use Requires monitoring if used long-term	[40, 49, 50]

Table 1 continued

Corticosteroid	Route/formulation + concentration	Mechanism / Key features	Safety	References
Prednisone	Systemic (oral) (mg dosing; not % formulation)	Synthetic glucocorticosteroid, derivative of cortisol Systemic glucocorticoid used when ocular disease is part of systemic autoimmune activity Oral prodrug converted to prednisolone Broad anti-inflammatory and immunosuppressive action Inhibits leukocyte migration, cytokine production (ILs, IFN-γ, TNF-α), and arachidonic pathways	Systemic adverse effects Possible corneal stromal and subepithelial deposits Requires monitoring if used long-term	[51]
Methylprednisolone aceponate	Systemic (oral)	Systemic glucocorticoid used for systemic autoimmune control (when indicated) Exhibits four times the potency of hydrocortisone Exerts DNA-level activity Inhibits cytokines and inflammatory mediators Reduces immune cell migration and activation	Less sodium/water retention than prednisone Reduced HPA axis suppression Fewer endocrine-related adverse effects	[37]
Dexamethasone	Topical ophthalmic solution/suspension; 0.1%	Synthetic corticosteroid Penetrates ocular tissues effectively Strong anti-inflammatory and anti-allergic effect Inhibits cytokines, leukotrienes, and histamine	High risk of IOP elevation with long-term use Risk of cataract formation	[37]

Table 1 continued

Corticosteroid	Route/formulation + concentration	Mechanism / Key features	Safety	References
Difluprednate	Topical ophthalmic emulsion; 0.05%	Exhibits very high potency (56 times greater receptor binding affinity than prednisolone acetate) Difluorinated prednisolone derivative Shows excellent tissue penetration and bioavailability, with prolonged effects Active metabolite has high glucocorticoid receptor affinity Allows reduced dosing frequency	High risk of IOP elevation and steroid response Requires close monitoring	[41, 52–54]

HPA hypothalamic–pituitary–adrenal axis; *IFN-γ* interferon-gamma; *ILs* interleukins; *IOP* intraocular pressure; *TNF-α* tumor necrosis factor-alpha

use the lowest effective dose for the shortest duration necessary, with close monitoring for potential adverse events. Prolonged systemic corticosteroid exposure can suppress the hypothalamic–pituitary–adrenal axis, and abrupt discontinuation can precipitate adrenal insufficiency or adrenal crisis [70, 71]. Additionally, discontinuation can lead to reactivation of the underlying condition for which glucocorticoids were prescribed. Although tapering is commonly practiced to mitigate these risks, there is a lack of evidence-based guidelines on how to taper systemic glucocorticoids effectively and safely [72]. Morning administration of short- or intermediate-acting corticosteroids such as hydrocortisone or prednisolone is preferred to mimic endogenous cortisol secretion. In high-risk patients or those exhibiting symptoms of adrenal insufficiency during tapering, evaluation of the hypothalamic–pituitary–adrenal axis function using basal and/or stimulated serum cortisol may guide further management [72]. While topical corticosteroids provide rapid and effective symptom relief in DED, especially in severe or refractory cases, their potential for adverse effects necessitates cautious and individualized use. Short-term treatment, preference for low-potency formulations, and implementation of appropriate tapering strategies are essential for balancing therapeutic efficacy with safety.

Nonsteroidal Anti-Inflammatory Drugs

In addition to corticosteroids, other classes of anti-inflammatory agents include nonsteroidal anti-inflammatory drugs (NSAIDs), such as ketorolac, nepafenac, diclofenac, and bromfenac [9]. Compared to corticosteroids, NSAIDs avoid steroid-associated IOP elevation, but their immunomodulatory effect is generally weaker than corticosteroids in inflammatory DED, and adverse corneal events (including delayed epithelial healing and rare corneal melt) have been reported in susceptible patients [21, 22, 73]. Agents such as ketorolac tromethamine exert their effect by inhibiting cyclooxygenase enzymes, thereby suppressing prostaglandin synthesis. This mechanism helps limit the migration and phagocytic activity of granulocytes and monocytes, contributing to the

control of inflammation on the ocular surface [74]. However, in cases of DED associated with autoimmune conditions (e.g., SS or RA), NSAIDs demonstrate significantly weaker immunomodulatory activity than corticosteroids. Additionally, they have been linked to delayed corneal epithelial healing and reduced corneal sensitivity. These adverse effects, particularly in patients undergoing ocular surgery or in those with autoimmune-related DED, have resulted in rare but severe complications such as corneal melting and even perforation [75].

Immunomodulators

Immunomodulators that target T-cell activation—such as CsA and tacrolimus, both calcineurin inhibitors, and lifitegrast, a lymphocyte function-associated antigen-1 (LFA-1) antagonist—play a crucial role in the long-term control of inflammation in DED [9, 22].

Cyclosporine A

CsA is a well-established calcineurin inhibitor that modulates T-cell–mediated inflammation by suppressing the transcription of pro-inflammatory cytokines such as IL-2 and interferon-gamma (IFN-γ) [76][29, 77]. In the context of DED, CsA reduces ocular surface lymphocyte activation, promotes goblet cell recovery, and helps restore tear film and conjunctival epithelial homeostasis [76] [77]. CsA inhibits calcineurin-dependent T-cell activation, thereby reducing IL-2–driven inflammatory signaling and downstream ocular surface inflammation [76] [29]. CsA also decreases IL-6 levels and reduces the expression of both inflammatory and apoptotic markers [76].

The efficacy of topical CsA in DED has been demonstrated in randomized controlled trials and meta-analyses. In multicenter randomized studies evaluating CsA ophthalmic emulsion in moderate-to-severe DED, treatment improved objective parameters such as corneal staining and Schirmer test outcomes, with symptom improvement in a subset of patients over time [78]. Multiple reports of clinical evidence support improvements in corneal staining, tear production measures, and symptoms in subsets of patients over time [76, 79, 80]. Newer formulations, including CsA 0.1% cationic emulsion (Ikervis®) and CsA 0.09% nanomicellar solution (Cequa®), provide enhanced ocular bioavailability and may offer faster or improved clinical efficacy [78, 81]. Because approved CsA products differ by concentration, formulation, and labeled dosing, dosing recommendations should be aligned with the specific formulation and regulatory label. In Europe, Ikervis® is labeled as one drop once daily at bedtime for adult patients with severe keratitis in DED not improving despite tear substitutes, with reassessment recommended at least every 6 months [79]. In the United States, Cequa® is labeled as one drop twice daily (approximately 12 h apart) into each eye and may be used concomitantly with tear substitutes with a 15-min interval between the instillations of the products [80]. Accordingly, in clinical practice, CsA dosing is most commonly once daily or twice daily depending on the formulation and label, while higher-frequency regimens are generally off-label strategies reserved for selected severe, refractory cases. Evidence suggests that off-label increased dosing frequency up to four times daily may accelerate symptom relief compared to standard twice-daily regimens, particularly during the induction phase or in patients unresponsive to standard regimens [82, 83]. Importantly, increasing dosing frequency does not significantly raise the risk of systemic side effects due to the minimal systemic absorption [84]. Conversely, higher CsA concentrations (e.g., >0.1%) do not appear to offer additional therapeutic benefits and may increase adverse sensations, such as ocular stinging or burning [84]. Therefore, the optimal balance between efficacy and tolerability is generally achieved with CsA concentrations between 0.05% and 0.1% [84]. Besides concentration, clinical differences also depend on formulation, dosing, and the population studied. In the pivotal phase 3 trials of twice-daily oil-in-water CsA emulsions, both CsA 0.05% and 0.1% improved objective signs (including corneal staining and categorized Schirmer outcomes) versus vehicle, with no clear dose–response relationship. CsA 0.05% also showed statistically significant improvement versus vehicle in several subjective outcomes [80]. Evidence directly comparing 0.05% and 0.1% in the same clinical context remains

limited. In a retrospective Sjögren's syndrome cohort, CsA 0.1% was associated with greater improvements in multiple inflammatory DED parameters than CsA 0.05% over 1–3 months, but discontinuation was higher with 0.1%, consistent with a potential tolerability trade-off [85].

CsA typically has a delayed onset (often several weeks), and short-term corticosteroids are often used at initiation to provide more immediate symptom relief [80, 86, 87]. The most commonly reported side effects of CsA include burning or stinging sensations upon instillation, conjunctival hyperemia, foreign body sensation, visual disturbances, ocular discharge, eye pain, and itching [10, 29, 88]. These adverse effects may affect treatment adherence, particularly during the early stage of therapy. Although the systemic route is associated with carcinogenic risk in some contexts, available literature has not demonstrated evidence of an increased risk of ocular surface neoplasia with topical ocular cyclosporine, since published reports are rare and do not establish causality [89]. Continued clinical vigilance is reasonable, particularly in patients with additional ocular surface squamous neoplasia (OSSN) risk factors or prior ocular surface dysplasia [89].

Tacrolimus

Tacrolimus, another calcineurin inhibitor, acts similarly to CsA by inhibiting calcineurin and downstream T-cell activation [29]. It is available in both eye drop and ointment formulations [29]. In DED, tacrolimus reduces T-cell–mediated ocular surface inflammation and may improve symptoms and tear parameters in severe/refractory disease [9, 29, 90]. Its efficacy has been demonstrated in severe and refractory cases of DED, particularly in those associated with chronic ocular graft-versus-host disease (GVHD) [91] and SS [92]. Studies comparing tacrolimus 0.03% with CsA 0.05% eye drops have shown comparable efficacy in improving symptoms without significant differences between the two agents [92]. Tacrolimus eye drops are generally well tolerated, although some patients report transient burning sensations, typically unrelated to efficacy [93]. Access is often through compounding preparations in some settings. Recently, developed drug delivery systems, such as cationic liposomes and gellan gum nanoparticles, have improved ocular penetration and bioavailability, helping to overcome tacrolimus' poor aqueous solubility and limited ocular permeability [29, 94]. Similar to CsA, long-term use of topical tacrolimus may alter immune regulation on the ocular surface and, at least theoretically, attenuate antiviral and antitumor immune surveillance [29, 95]. However, evidence directly linking topical tacrolimus to OSSN is very limited and largely restricted to isolated case reports in patients with substantial baseline risk factors (e.g., severe atopic ocular disease and/or systemic immunosuppression) [29, 96, 97]. These concerns are therefore mostly theoretical and extrapolated from broader immunosuppression contexts and from regulatory cautions for topical calcineurin inhibitors used in other indications [98]. In clinical practice, expert reviews recommend regular follow-up during long-term topical immunosuppressive therapy, with heightened vigilance in patients who already carry recognized OSSN risk factors, such as prior ocular surface dysplasia/OSSN, substantial ultraviolet exposure, or immunocompromised states [99]. In cases of suspected OSSN, immunosuppressive therapy should be discontinued promptly, and appropriate diagnostic investigations should be initiated.

Lifitegrast

Lifitegrast is a novel immunomodulatory agent with a distinct mechanism of action. It targets LFA-1, inhibiting its binding to intercellular adhesion molecule-1 (ICAM-1) [29, 100, 101]. By blocking LFA-1/ICAM-1 interaction, lifitegrast reduces T-cell–associated ocular surface inflammation [102, 103].

Several phase III trials and other clinical studies have demonstrated that lifitegrast improves both subjective symptoms (e.g., ocular discomfort, dryness, and foreign body sensation) and objective signs (e.g., corneal fluorescein staining, and TBUT) [29, 104, 105]. Lifitegrast is generally well tolerated [29]. The most common ocular side effects include transient mild-to-moderate irritation, blurred vision, and dysgeusia (altered taste), with the latter occurring in approximately 12.9% of patients [29, 103, 105]. Compared to CsA, lifitegrast may offer a more favorable tolerability profile, particularly in patients sensitive to burning or stinging sensations from other

medications [106]. No systemic toxicity or secondary infections have been associated with lifitegrast use [9].

Antibiotics, omega-3 polyunsaturated fatty acids, and biological tear substitutes

The two primary classes of antibiotics used in the management of DED owing to MGD are tetracyclines and macrolides. These agents are employed not only for antimicrobial properties but also for their immunomodulatory and meibum-modulating effects. Tetracyclines, especially the second-generation doxycycline, exhibit anti-inflammatory activity that makes them valuable adjuncts in the treatment of various types of ocular surface diseases. They inhibit MMPs, suppress pro-inflammatory cytokine release, and reduce both ocular surface inflammation and MGD [9]. Low-dose doxycycline (20–50 mg/day) is commonly prescribed for DED associated with ocular rosacea or posterior blepharitis [107, 108]. For MGD-related evaporative DED, systemic tetracyclines (especially doxycycline) are commonly used as adjunct therapy, largely for their anti-inflammatory and antilipase effects rather than for antimicrobial activity [109]. In randomized and comparative studies, oral doxycycline has been administered for ~4 weeks (e.g., 100 mg twice daily for 4 weeks) and for 6 weeks in moderate–severe or refractory MGD (e.g., 200 mg/day for 6 weeks) [110, 111]. Sub-antimicrobial dosing has also been evaluated in chronic/refractory MGD (e.g., doxycycline 20 mg twice daily for 1 month) [112]. Clinical studies have demonstrated improvements in tear film stability, lid margin inflammation, and subjective symptom scores following several weeks of therapy [109]. However, gastrointestinal side effects and photosensitivity may limit long-term use and tolerability, particularly at higher doses. Macrolides also exert significant immunomodulatory effects. Azithromycin has been shown to reduce ocular surface leukocyte infiltration and downregulate pro-inflammatory cytokine and MMP expression in the skin and tear film [113]. Azithromycin can be used both orally or topically, and the administration route should be specified because regimens differ substantially. Concerning systemic therapy, randomized studies have evaluated short-course oral azithromycin (e.g., 500 mg on day 1 followed by 250 mg/day for four additional days) compared to doxycycline 200 mg/day for 6 weeks in MGD, showing equivalent effects or even better results on signs for azithromycin [111, 114]. A recent meta-analysis comparing the pooled effects of systemic macrolides and tetracyclines on MGD- and DED-related signs and symptoms demonstrated the superior efficacy and safety profile of the former class [115]. Concerning topical therapy, a randomized trial compared azithromycin 1.5% eye drops twice daily for 2 days followed by once daily up to 4 weeks to oral doxycycline for 4 weeks in moderate–severe MGD, showing similar results [110].

Omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic and docosahexaenoic acids, have been investigated for their potential anti-inflammatory effects in DED. These fatty acids may improve meibomian gland function and modulate inflammatory mediator production at the ocular surface [116]. Some randomized controlled trials have demonstrated benefits in symptom relief and tear film stability, while others, such as the large DREAM study, reported no significant advantage over placebo [117]. Despite controversial evidence, dietary supplementation with omega-3 polyunsaturated fatty acids remains a commonly recommended adjunctive therapy, particularly in patients with EDE.

Tear substitutes, while primarily providing symptomatic relief, play a supportive role in managing ocular surface inflammation. Preservative-free formulations help dilute pro-inflammatory cytokines and reduce tear film osmolarity, thereby indirectly mitigating epithelial stress [14]. Some newer tear substitutes are enriched with anti-inflammatory components such as desonide sodium phosphate 0.025%, hydrocortisone 0.001%, trehalose, and *Aloe vera*, which aid in restoring ocular surface homeostasis and reducing oxidative damage [118–121]. Although not curative, the regular use of appropriate tear substitutes improves ocular comfort, supports healing, and enhances the effectiveness of concurrent pharmacologic treatments. In patients with severe DED and compromised ocular surface status, biological tear replacements, including autologous or allogeneic serum tears, autologous platelet lysate, platelet-rich plasma

(PRP), cord blood serum, and amniotic membrane extract eye drops, offer both regenerative and anti-inflammatory benefits. These preparations contain growth factors, anti-inflammatory cytokines (e.g., IL-1Ra, soluble TNF receptors, MMP inhibitors), and other bioactive molecules that stimulate the healing of the epithelia and modulate the ocular surface immune response [9]. Their use is particularly beneficial in severe or refractory cases owing to ocular GVHD and autoimmune conditions (e.g., SS).

Expert Recommendations on Treatment Strategies Based on Challenging Cases

Long-term management of inflammation in severe DED requires a structured, stepwise approach guided by disease severity, underlying pathophysiology, and patient-specific factors [2, 26]. While tear substitutes remain the mainstay of therapy, effective long-term control increasingly depends on targeting ocular surface inflammation and MGD [21]. First-line strategies, including patient education, environmental modification, eyelid hygiene, and preservative-free tear substitutes, are widely adopted globally [21, 122–126].

Anti-inflammatory and immunomodulatory therapies are crucial for long-term disease control. Agents such as CsA, lifitegrast, and tacrolimus are increasingly prescribed across diverse DED subtypes, reflecting clinician confidence in their safety and efficacy [127]. Among these, tacrolimus has seen greater global adoption, likely due to its favorable risk–benefit profile. Topical corticosteroids, such as loteprednol and fluorometholone, are used short-term for exacerbations, while Eysuvis®, the first FDA-approved corticosteroid for DED, is indicated for intermittent use. Stronger corticosteroids such as dexamethasone require cautious application due to risks such as elevated IOP [29]. Systemic anti-inflammatory agents are indicated in cases of DED associated with autoimmune diseases. Immunosuppressants such as rituximab, methotrexate, and mycophenolate mofetil help control systemic inflammation and often lead to ocular improvement [128]. Concurrently, local treatments, including tear substitutes and topical CsA, remain essential to supporting and maintaining ocular surface integrity.

A comprehensive treatment strategy that integrates both systemic and ocular approaches improves outcomes, reduces symptom burden, and enhances quality of life. Long-term management should also include routine monitoring to detect adverse effects and guide therapy adjustments [129]. Treatment selection varies according to DED subtype: ADDE is more often treated with punctal occlusion, secretagogues, and therapeutic contact lenses, while EDE benefits from lipid-based products, lid hygiene, and warming therapies [127]. These interventions are aimed at restoring meibomian gland function, reducing ductal obstruction, and re-establishing lipid layer integrity to reduce tear evaporation [127]. The management of EDE also includes in-office treatments such as intense pulsed light, low-level light therapy, and devices for inner lid warming and massage [130–133]. Systemic antibiotics (e.g., doxycycline, azithromycin) are used for their anti-inflammatory effects, although concerns remain regarding resistance and long-term benefits [29]. For advanced or refractory cases, additional options include biological tear substitutes (e.g., autologous serum, PRP), punctal occlusion, therapeutic contact lenses, and amniotic membrane extracts or grafts [21, 134]. Goblet cell dysfunction, a hallmark of severe DED, may be reversed with CsA, which has been shown to restore goblet cell density over 6 to 12 weeks [135].

Sjögren Syndrome

SS is a chronic, systemic autoimmune disease that primarily targets the exocrine glands, leading to reduced tear and saliva production. It affects approximately 60 per 100,000 people globally, with a strong female predominance [136–138]. Ocular involvement, particularly DED, is one of the hallmarks of SS and often presents more severely than in non-SS DED, typically involving both ADDE and EDE subtypes [137, 139]. Common symptoms include burning, irritation, foreign body sensation, photophobia, excessive tearing, and visual disturbances, particularly when triggered by environmental factors [140–142]. Patients

often demonstrate markedly low Schirmer test values, short TBUT, and positive fluorescein staining of the cornea. Additional findings include filamentary keratitis, mucous plaques, ocular hyperemia, and conjunctival folds. MGD is consistently observed, characterized by gland obstruction, dropout, and atrophy. In advanced stages, patients may develop serious complications such as persistent epithelial defects and corneal ulceration, which may progress to perforation requiring urgent surgical intervention.

SS-related DED is clinically complex, often refractory to conventional therapy, and can lead to vision-threatening complications if not managed through a multidisciplinary treatment strategy. The recommended treatment for SS-related DED involves a multifaceted, stepwise approach targeting both tear film instability or deficiency and chronic ocular surface inflammation [29, 143, 144]. Core therapy includes frequent use of preservative-free tear substitutes and vitamin A ointment at nighttime to promote epithelial healing and protect ocular surface. In moderate-to-severe cases, blood-derived eye drops (e.g., PRP) are recommended to support tissue repair. Topical CsA (e.g., Ikervis®) remains the cornerstone of long-term anti-inflammatory therapy and should be administered once daily on a chronic basis. During acute exacerbations, short courses of topical corticosteroids (e.g., dexamethasone) may be added to rapidly reduce inflammation. For patients with systemic involvement or insufficient response to topical therapy, systemic immunosuppressants such as azathioprine may be prescribed in collaboration with a rheumatologist [29, 143, 144]. Management of MGD, which is frequently observed in SS, is also critical and includes daily eyelid hygiene and warm compresses at approximately 40 °C. In advanced cases involving corneal ulceration or perforation, surgical interventions such as amniotic membrane transplantation or, when necessary, penetrating keratoplasty are indicated. Active patient participation in self-care, alongside interdisciplinary collaboration, is essential for addressing both ocular and systemic manifestations of SS-related DED [145].

Other Autoimmune Diseases

DED is one of the most frequent ocular manifestations associated with autoimmune diseases, including not only SS but also RA, SLE, and systemic sclerosis [146]. In RA, DED is the most common ocular complication, followed by episcleritis, scleritis, and peripheral ulcerative keratitis [147]. The severity of DED in the setting of RA correlates more closely with disease duration than with systemic disease activity, and may occur independently of joint involvement [148]. DED in RA can present with or without secondary SS and is significantly more common in women (female-to-male ratio of 9:1), typically manifesting as a mixed form of DED [145, 149]. In SLE, DED is also among the most prevalent ocular manifestation, with reported prevalence rates ranging from 13.4% to 39.5% [150, 151]. Ocular surface damage in SLE results from lacrimal gland dysfunction, reduced corneal sensitivity, meibomian gland abnormalities, and increased Langerhans cells, leading to epithelial apoptosis and keratitis [146, 152]. In severe cases of SLE, complications such as neurotrophic keratopathy and peripheral ulcerative keratitis may develop [153, 154]. Across these autoimmune diseases, the pathogenesis of DED involves both innate and adaptive immune responses. Key mechanisms include activation of Th1 and Th17 lymphocytes, overproduction of IFN-γ leading to goblet cell loss, and infiltration of lacrimal and conjunctival tissues by T cells, causing glandular apoptosis, fibrosis, and reduced tear production [14, 155–157].

The recommended treatment regimen for autoimmune-related DED in the context of RA involves a structured, multistep approach aimed at reducing ocular surface inflammation, improving tear film quality, and restoring epithelial integrity. First-line therapy includes the frequent and regular use of preservative-free tear substitutes, along with warm compresses, eyelid hygiene, and bedtime application of vitamin A ointment to support epithelial healing and manage MGD. In RA patients, punctal plugs may be added to enhance tear retention. Insufficient response to lubricants alone may require the addition of topical CsA 0.1% once daily as a long-term anti-inflammatory treatment.

Case Presentation

In the following section, we describe five complex cases of autoimmune-related DED that illustrate the challenges associated with effective management for obtaining acceptable outcomes.

Case #1

A 56-year-old woman with severe DED secondary to SS had been monitored semi-annually over 5 years. Her condition remained clinically stable, with bilateral MGD and punctate keratopathy, along with filamentary keratitis in the left eye (Fig. 1A). Symptoms were initially managed with preservative-free tear substitutes, heated eye mask at bedtime, and intermittent courses of corticosteroids to control inflammatory flare-ups. At presentation, the patient reported severe ocular redness and decreased vision. Clinical examination revealed a large corneal epithelial defect measuring 7.5 × 7.5 mm (Fig. 1B), accompanied by significantly reduced corneal sensitivity, as measured by Cochet–Bonnet esthesiometry (10 mm). Despite conservative treatment, the condition progressed over the following 2 weeks to a central corneal perforation (1.0 × 1.0 mm) with iris prolapse and surrounding area of keratolysis measuring 2.5 × 2.5 mm (Fig. 1C). A Gundersen conjunctival autograft was performed to provide tectonic support (Fig. 1D). Postoperatively, preservative-free tear substitutes were maintained and topical CsA was initiated once daily for long-term control of ocular surface inflammation; an antibiotic-corticosteroid combination was used four times for 7 days. At 4 months, ocular inflammation had improved sufficiently, and thus optical penetrating keratoplasty was performed. However,

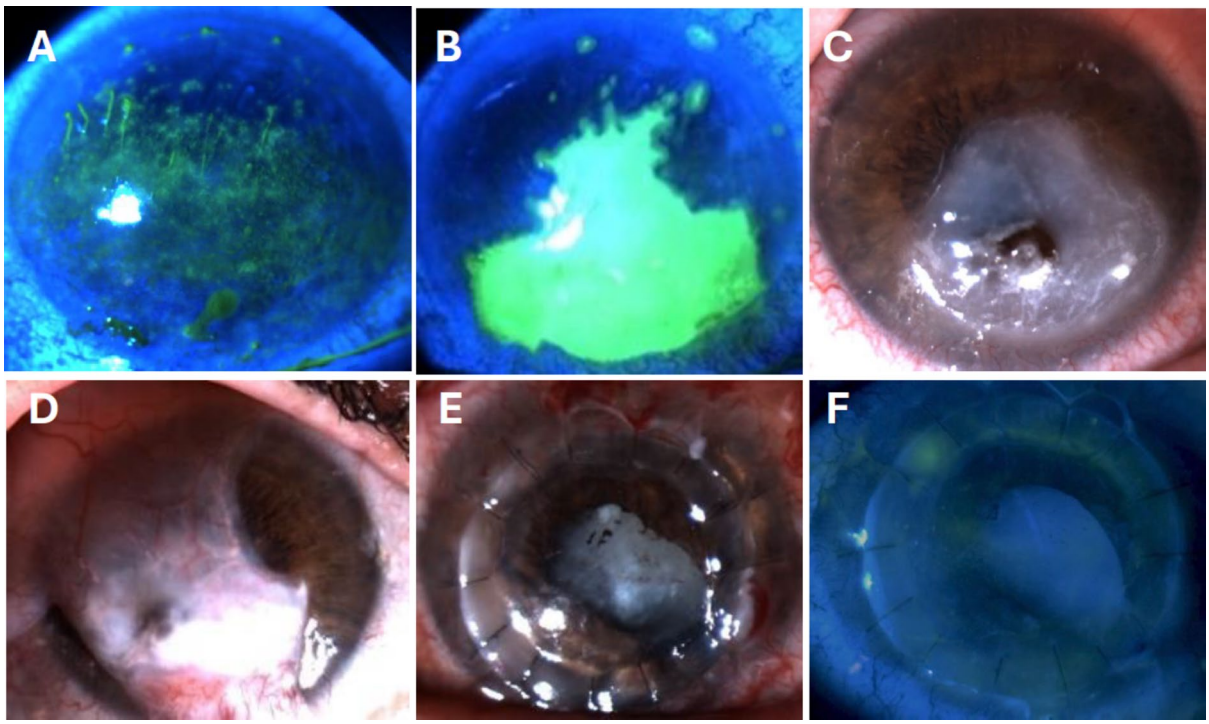

Fig. 1 Clinical pictures of the left eye of a 56-year-old woman with severe dry eye owing to Sjögren's syndrome. Punctate keratopathy with abundant filamentary keratitis (**A**). Large corneal epithelial defect (7.5 × 7.5 mm) complicated by reduced corneal sensitivity (**B**). Central corneal perforation (1.0 × 1.0 mm) with iris prolapse and a surrounding area of keratolysis (2.5 × 2.5 mm) (**C**). Gundersen conjunctival autograft performed for tectonic support (**D**). Clear penetrating keratoplasty graft; a mature cataract is visible (**E**). Six months postoperatively, the corneal graft was clear and epithelized (**F**)

postoperative visual recovery was limited by the presence of a mature cataract (Fig. 1E). By 6 months postoperatively, the ocular surface remained stable and the corneal graft was clear and fully epithelized (Fig. 1F); the conditions of the fellow eye remained stable, with only mild punctate keratopathy.

Case #2

A 66-year-old patient with DED secondary to RA and SS, on long-term systemic immunosuppression (methylprednisolone and methotrexate), presented with chronic bilateral keratitis unresponsive to previous treatments. Clinical examination revealed severe ocular surface disease with corneal epithelial defects and stromal infiltrates (Fig. 2A, B). Due to clinical suspicion of fungal keratitis, topical fluconazole 0.2% (six times daily) was initiated. Over the following weeks, inflammation subsided and corneal epithelialization was achieved, although peripheral opacities persisted (Fig. 2C, D). To obtain sustained inflammation control and improve tear film parameters (Schirmer test, 1 mm/5 min; TBUT, 2 s in both eyes), long-term topical therapy with CsA (Ikervis®) once daily and tear substitutes was initiated. During exacerbations, the patient received topical dexamethasone 0.1% four times daily for 2 weeks followed by a 1-month course of topical prednisolone 1% tapered from twice daily to once daily. The patient tolerated CsA eye drops well, with notable symptom relief. After 8 months of therapy, the ocular surface stabilized but lens opacification was present. Prior to cataract surgery, a 3-week course of PRP eye drops was added. Postoperatively, both eyes developed ocular surface impairment with filamentary keratitis (Fig. 2E, F), which was managed with intensive lubrication and extended corticosteroid therapy—initially dexamethasone, followed by prednisolone. This regimen led to corneal re-epithelialization and reduced inflammation within 3 months after surgery. At the 2-year follow-up, the ocular surface remained stable under CsA treatment on a chronic basis (Fig. 2 G, H), with best-corrected visual acuity of 0.6 in the right eye and 0.2 in the left.

Case #3

A 68-year-old man with a history of SS-associated DED and prior bilateral amniotic membrane

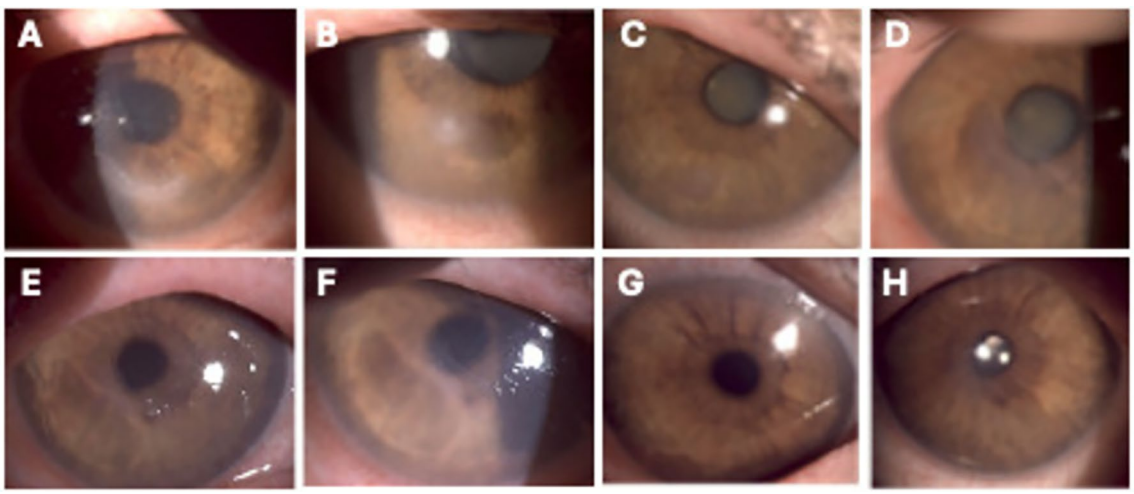

Fig. 2 Clinical pictures of both eyes of a 66-year-old patient with dry eye owing to rheumatoid arthritis and secondary Sjögren's syndrome, with chronic bilateral keratitis unresponsive to previous treatments. Severe ocular surface disease with corneal epithelial defects and stromal infiltrates (**A**, **B**). Corneal epithelialization was achieved, with the presence of peripheral opacities (**C**, **D**). After uneventful cataract surgery, ocular surface disease worsened with the onset of filamentary keratitis (**E**, **F**). After 2 years of topical treatment with cyclosporine A, progressive improvement of the ocular surface status (**G**, **H**)

transplantation presented urgently with acute vision loss and pain in the right eye. He had not used ophthalmic medications or attended follow-up appointments for several years. Clinical examination revealed a perforated corneal ulcer in the right eye, with iris prolapse, complete anterior chamber collapse, and a mature cataract (Fig. 3A). The contralateral eye exhibited signs of corneal thinning and vascularization. The patient was admitted, and systemic doxycycline, topical levofloxacin, and preservative-free tear substitutes were prescribed. Due to the severity of the right eye's condition, a staged surgical approach was adopted. Amniotic membrane transplantation was performed to stabilize the ocular surface while awaiting donor corneal tissue for definitive transplantation. Subsequently, a triple procedure involving penetrating keratoplasty, cataract extraction, and intraocular lens implantation was successfully performed in the right eye (Fig. 3B). Postoperative treatment included topical moxifloxacin, dexamethasone, and tear substitutes, along with temporary punctal plugs. Ten days later, corneal perforation occurred in the left eye (Fig. 3C). A localized amniotic membrane patch was applied using a multilayer "sandwich" technique (Fig. 3 D). The patient was discharged with systemic therapy comprising azathioprine, methylprednisolone, and doxycycline. Topical treatment included moxifloxacin four times daily for 7 days, CsA once daily, and tear substitutes six times daily in both eyes. Dexamethasone eye drops were prescribed only in the transplanted eye (four times daily). Systemic methylprednisolone, doxycycline, and topical dexamethasone were gradually

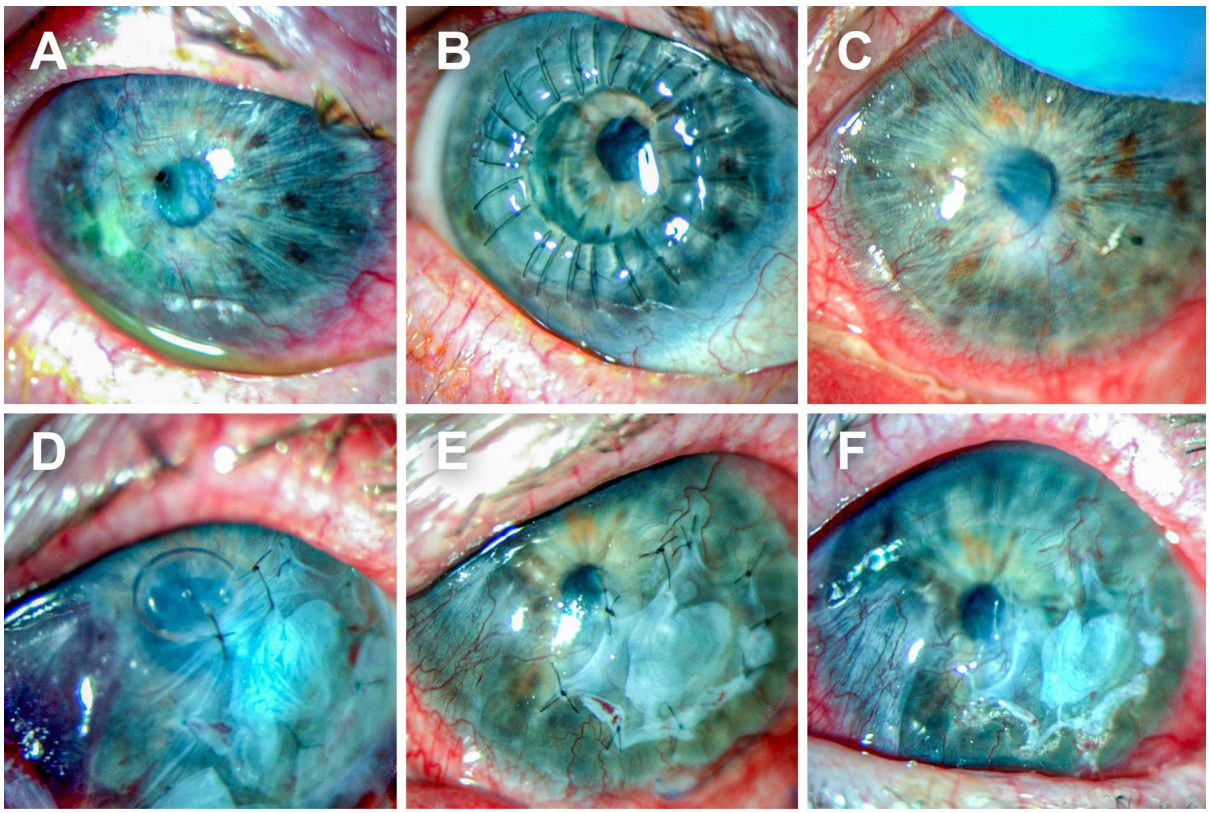

Fig. 3 Clinical pictures of both eyes of a 68-year-old man with a history of SS–associated dry eye. Corneal perforation in the site of a sterile corneal ulceration with thinning (right eye) (**A**). Postoperative appearance after triple procedure—penetrating keratoplasty with cataract surgery and intraocular lens implantation (**B**). Corneal perforation in the site of a sterile corneal ulceration with thinning (left eye) (**C**). Appearance of the corneal surface 1 week (**D**), 1 month (**E**), and 3 months (**F**) after localized amniotic membrane patch and multilayer "sandwich" technique

tapered, while azathioprine, topical CsA, and preservative-free tear substitutes were continued as part of long-term maintenance therapy. Amniotic membrane transplantation successfully restored corneal integrity, as confirmed at 1- and 3-month follow-up visits (Fig. 3 E, F). At the last follow-up, the patient was asymptomatic and tolerated the treatment well, and best-corrected visual acuity had improved to 0.2 in both eyes.

Case #4

A 60-year-old woman with DED secondary to RA presented with progressive visual decline, dryness, irritation, and photophobia, unrelieved by the intense use of tear substitutes. Slit-lamp examination revealed severe DED with MGD, low tear production (Schirmer test, 1 mm/5 min bilaterally), positive corneal fluorescein staining, and conjunctival redness (Fig. 4A, B). A diagnosis of secondary SS was confirmed by laboratory testing and salivary gland biopsy. Initial treatment included eyelid hygiene and topical therapy with tear substitutes, PRP eye drops five times daily, 1-week course of hydrocortisone four times, vitamin A ointment at bedtime, and CsA (Ikervis®) once daily. Systemic immunosuppressive treatment was initiated in coordination with the rheumatologist. After 12 weeks, visual

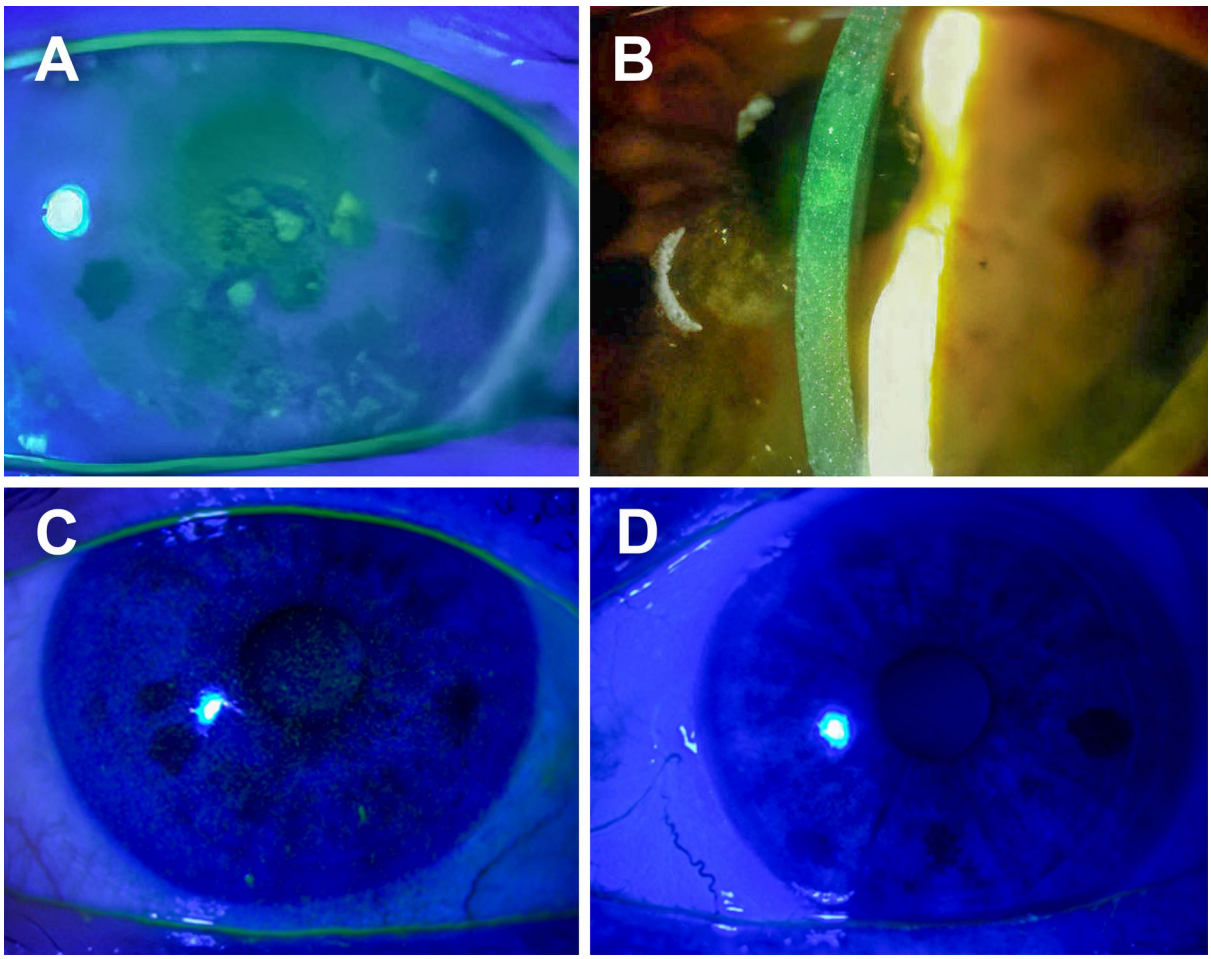

Fig. 4 Clinical pictures of both eyes of a 60-year-old woman affected by dry eye owing to rheumatoid arthritis. Slit-lamp examination results before the treatment. Diffuse punctate keratopathy at presentation (**A**, **B**). Significant decrease in corneal fluorescein staining after 12 weeks of treatment with platelet-rich plasma eye drops, vitamin A ointment, and cyclosporine A eye drops (**C**, **D**)

acuity improved in both eyes, Schirmer values increased to 4 mm/5 min in the right eye and 5 mm/5 min in the left, and corneal fluorescein staining decreased, particularly in the left eye (Fig. 4 C, D). The patient also reported significant symptomatic relief, and long-term topical therapy, including CsA, was continued without modification.

Case #5

A 64-year-old woman with a long-standing history of seropositive RA presented with worsening ocular symptoms, including irritation, burning, and foreign body sensation in both eyes, despite stable systemic treatment with methotrexate and low-dose prednisone. Slit-lamp examination revealed significant corneal fluorescein staining and conjunctival hyperemia in both eyes. Tear production was reduced (Schirmer test < 5 mm/5 min), and tear film instability was evident (average noninvasive BUT of 1.3 s) (Fig. 5A). Initial treatment included preservative-free tear substitutes containing hyaluronic acid (0.2%) and ectoine (2.0%), warm compresses, and punctal plugs. However, due to insufficient response, topical CsA 0.1% (Ikervis®) was initiated once daily to control ocular surface inflammation. At the 3-month follow-up, the patient demonstrated notable clinical improvement, with reduced values of corneal fluorescein staining and conjunctival hyperemia. Schirmer values improved to 8 mm/5 min, and average noninvasive BUT increased to 11.5 s (Fig. 5B). In parallel, the Ocular Surface Disease Index (OSDI) score decreased from 45 to 23. The patient tolerated CsA well and continued it chronically in combination with preservative-free tear substitutes.

DISCUSSION

DED is a chronic inflammatory disorder of the ocular surface, with inflammation playing a central role in its pathogenesis, progression, and complications [14]. The cases presented in this article highlight the clinical relevance of persistent inflammation in autoimmune-associated DED and underscore the importance of targeted, sustained immunomodulatory therapy to achieve long-term disease control. Uncontrolled ocular surface inflammation perpetuates a vicious cycle of tear film instability, epithelial cell damage, and goblet cell loss, which may ultimately lead to corneal neovascularization and opacity if not appropriately managed [68, 158]. In this context, long-term control of inflammation is not only symptom- but also

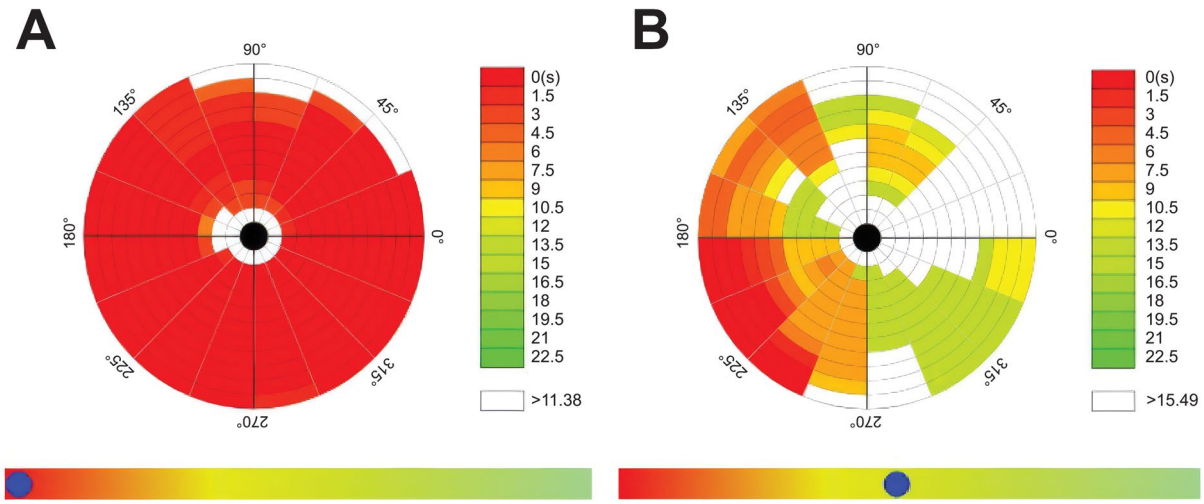

Fig. 5 Graphical maps of average noninvasive breakup time test showing a significant improvement from the baseline value of 1.3 s (**A**) and the follow-up value of 11.5 s after 3 months of therapy with topical cyclosporine A 0.1% (**B**)

disease-modifying, with the potential to halt or reverse the negative effects of chronic immune activation. As confirmed in the cases presented above, topical CsA is a well-studied option for sustained inflammatory control in DED and has been associated with improvements in ocular surface integrity and tear film-related metrics in appropriately selected patients [76, 135].

Clinical studies have confirmed the efficacy and safety of CsA formulations in the treatment of DED. Ikervis® (CsA 0.1% cationic emulsion) demonstrated significant improvements in corneal fluorescein staining and ocular surface inflammation compared to vehicle in a multicenter, randomized phase III trial [159, 160]. These findings are supported by real-world data, which show sustained improvements in corneal damage, TBUT, and ocular redness starting from week 4 and maintained through 12 months of treatment [161]. The long-term safety and efficacy of CsA 0.1% cationic emulsion are further substantiated by a systematic review summarizing evidence from randomized controlled trials and real-life studies [162]. However, due to its delayed onset of action, typically 8–12 weeks, short-term corticosteroids are often recommended during the induction phase to manage acute symptoms and promote early treatment adherence [87].

Selecting and managing treatment in chronic DED requires a structured and patient-specific approach. Initial therapy often includes short-term corticosteroids to rapidly suppress inflammation, followed by the introduction of CsA for long-term control [9]. Adjunctive therapies, such as preservative-free tear substitutes and consistent eyelid hygiene remain essential components of ongoing management [163]. In cases associated with MGD, systemic tetracyclines, including doxycycline, or azithromycin may provide additional benefit by inhibiting MMPs and reducing glandular inflammation [163].

Long-term management also necessitates regular monitoring, for both therapeutic efficacy and potential side effects, such as stinging or hyperemia, that may negatively affect patient adherence [99, 129]. Importantly, in contrast to corticosteroids, CsA is not associated with IOP elevation or cataract formation, which makes them a safer option for chronic use. Newer CsA formulations with improved tolerability (e.g., Cequa®, Ikervis®) have further improved patient adherence and clinical outcomes [78].

This work has several limitations that deserve mentioning. First, the clinical cases are heterogeneous with respect to autoimmune diagnosis, baseline severity, prior ocular history (including prior surgeries), and follow-up duration. Second, the management was multimodal (e.g., lubrication, lid therapy, punctal occlusion, blood-derived tear substitutes, topical antibiotics/antifungals, topical corticosteroids, and topical/systemic immunosuppression), precluding causal attribution of the improvement to any single agent. Third, prior treatments and delays in care may have influenced both baseline severity and subsequent clinical course. Consequently, the cases are best interpreted as real-world illustrations of stepwise care rather than comparative effectiveness evidence that any single treatment was responsible for the observed outcomes.

CONCLUSIONS

All cases presented herein involved progressive signs and symptoms of DED associated with autoimmune diseases and complicated by severe ocular surface inflammation and/or structural corneal complications. At presentation, patients were often managed with lubrication and supportive measures, combined in some cases with systemic immunosuppression for their underlying disease, but sustained topical anti-inflammatory maintenance therapy (e.g., topical CsA) and structured follow-up were frequently absent or inconsistent. In each case, appropriate treatment was initiated with a critical focus on sustained inflammation control. After switching to multimodal therapy focused on long-term ocular surface inflammation control (mainly based on CsA eye drops), lid-targeted measures, and systemic therapy (when indicated), ocular surface stability improved over the following months and was maintained for years. In some instances, urgent surgical intervention was required to preserve globe integrity.

Taken together, these cases underscore the role of long-term immunomodulatory therapy, with CsA as a central component, within a broader, individualized and stepwise strategy for managing severe and chronic DED in the setting of autoimmunity. Sustained control of ocular surface inflammation can alleviate symptoms, reduce the risk of irreversible ocular surface damage and complications, and support satisfactory quality of life, provided it is coupled with early recognition of inflammatory subtypes, tailored pharmacologic regimens, and regular clinical monitoring.

Medical Writing, Editorial, and Other Assistance. Medical writing assistance was provided by Proper Medical Writing, Warsaw, Poland. Funding was provided by Santen.

Author Contributions. Giuseppe Giannaccare—study concept and design, case description, preparation of the first draft of the manuscript, project supervision. Botagoz Issergepova—study concept and design, case description, revision of the first draft of the manuscript. Maciej Kozak—study concept and design, case description, revision of the first draft of the manuscript. Adriana Takáčová—study concept and design, case description, revision of the first draft of the manuscript. Dominika Wróbel-Dudzińska—study concept and design, case description, revision of the first draft of the manuscript. Gulnara Begimbayeva Yenbekovna—study concept and design, literature search, revision of the first draft of the manuscript. Camelia Margareta Bogdanici—study concept and design, literature search, revision of the first draft of the manuscript. Iryna Deryapa—study concept and design, literature search, revision of the first draft of the manuscript Kamila Kušev—study concept and design, literature search, revision of the first draft of the manuscript. Zoltán Nagy—study concept and design, literature search, revision of the first draft of the manuscript. Małgorzata Stawska—study concept and design, literature search, revision of the first draft of the manuscript. Luidmila Troychenko—study concept and design, literature search, revision of the first draft of the manuscript. Robert Rejdak—study concept and design, literature search, revision of the first draft of the manuscript. Tomasz Chorągiewicz—study concept and design, literature search, revision of the first draft of the manuscript, project supervision. All authors read and approved the final manuscript.

Funding. No funding or sponsorship was received for the publication of this article.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Giuseppe Giannaccare received a publication grant from Santen. Botagoz Issergepova received scientific consultation and lecture fees from Santen. B.I. is a member of the Expert Council on Corneal Pathology of the Kazakhstan Society of Ophthalmologists. Maciej Kozak, Dominika Wróbel-Dudzińska, Gulnara Begimbayeva Yenbekovna, Camelia Margareta Bogdanici, Iryna Deryapa, Kamila Kušev, Zoltán Nagy, Małgorzata Stawska, Luidmila Troychenko, Robert Rejdak, and Tomasz Chorągiewicz declare that they have no conflict of interest.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Written informed consent to publish the clinical details and any accompanying images was obtained from all patients and all data have been anonymized to protect patient confidentiality.

REFERENCES

1. Belmonte C, Nichols JJ, Cox SM, Brock JA, Begley CG, Bereiter DA, et al. TFOS DEWS II pain and sensation report. Ocul Surf. 2017;15:404–37.

2. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo C-K, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15:276–83. https://doi.org/10.1016/j.jtos.2017.05.008.

3. Kwon J, Moghtader A, Kang C, Bibak Bejandi Z, Shahjahan S, Alzein A, et al. Overview of dry eye disease for primary care physicians. Medicina. 2025;61:460.

4. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. Ocul Surf. 2017;15:334–65. https://doi.org/10.1016/j.jtos.2017.05.003.

5. Paulsen AJ, Cruickshanks KJ, Fischer ME, Huang GH, Klein BE, Klein R, et al. Dry eye in the Beaver Dam Offspring Study: prevalence, risk factors, and health-related quality of life. Am J Ophthalmol. 2014;157:799–806. https://doi.org/10.1016/j.ajo.2013.12.023.

6. Both T, Dalm VA, van Hagen PM, van Daele PL. Reviewing primary Sjögren's syndrome: beyond the dryness - from pathophysiology to diagnosis and treatment. Int J Med Sci. 2017;14:191–200. https://doi.org/10.7150/ijms.17718.

7. Ziaragkali S, Kotsalidou A, Trakos N. Dry eye disease in routine rheumatology practice. Mediterr J Rheumatol. 2018;29:127–39. https://doi.org/10.31138/mjr.29.3.127.

8. Gomes JAP, Azar DT, Baudouin C, Efron N, Hirayama M, Horwath-Winter J, et al. Tfos dews ii iatrogenic report. Ocul Surf. 2017;15:511–38.

9. Nguyen A, Kolluru A, Beglarian T. Dry eye disease: a review of anti-inflammatory therapies. Taiwan J Ophthalmol. 2023;13:3–12. https://doi.org/10.4103/2211-5056.369606.

10. de Oliveira RC, Wilson SE. <article-title updat e="added"><p>Practical guidance for the use of cyclosporine ophthalmic solutions in the management of dry eye disease</p>. Clin Ophthalmol. 2019;13:1115–22. https://doi.org/10.2147/opth.S184412.

11. Wolffsohn JS, Benítez-Del-Castillo J, Loya-Garcia D, Inomata T, Iyar G, Liang L, et al. TFOS DEWS III diagnostic methodology. Am J Ophthalmol. 2025. https://doi.org/10.1016/j.ajo.2025.05.033.

12. Tan X, Sun S, Liu Y, Zhu T, Wang K, Ren T, et al. Analysis of Th17-associated cytokines in tears of patients with dry eye syndrome. Eye Lond. 2014;28:608–13. https://doi.org/10.1038/eye.2014.38.

13. Belmonte C, Nichols JJ, Cox SM, Brock JA, Begley CG, Bereiter DA, et al. TFOS DEWS II pain and sensation report. Ocul Surf. 2017;15:404–37. https://doi.org/10.1016/j.jtos.2017.05.002.

14. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15:438–510. https://doi.org/10.1016/j.jtos.2017.05.011.

15. Kunert KS, Tisdale AS, Stern ME, Smith J, Gipson IK. Analysis of topical cyclosporine treatment of patients with dry eye syndrome: effect on conjunctival lymphocytes. Arch Ophthalmol. 2000;118:1489–96.

16. Golden MI, Meyer JJ, Zeppieri M, et al. Dry Eye Syndrome. [Updated 2024 Feb 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470411/.

17. Lixi F, Coco G, Corda C, Villani E, Curci A, Slidsborg C, et al. Light discomfort thresholds under different lighting conditions in healthy subjects and dry eye patients. Sci Rep. 2025;15:29213. https://doi.org/10.1038/s41598-025-15633-1.

18. Sullivan BD, Crews LA, Messmer EM, Foulks GN, Nichols KK, Baenninger P, et al. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. Acta Ophthalmol. 2014;92:161–6. https://doi.org/10.1111/aos.12012.

19. Mertzanis P, Abetz L, Rajagopalan K, Espindle D, Chalmers R, Snyder C, et al. The relative burden of dry eye in patients' lives: comparisons to a U.S. normative sample. Invest Ophthalmol Vis Sci. 2005;46:46–50. https://doi.org/10.1167/iovs.03-0915.

20. Ayaki M, Kawashima M, Negishi K, Kishimoto T, Mimura M, Tsubota K. Sleep and mood disorders

in dry eye disease and allied irritating ocular diseases. Sci Rep. 2016;6:22480. https://doi.org/10.1038/srep22480.

21. Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II Management and Therapy Report. Ocul Surf. 2017;15:575–628. https://doi.org/10.1016/j.jtos.2017.05.006.

22. Liu SH, Saldanha IJ, Abraham AG, Rittiphairoj T, Hauswirth S, Gregory D, et al. Topical corticosteroids for dry eye. Cochrane Database Syst Rev. 2022. https://doi.org/10.1002/14651858.CD015070.pub2.

23. Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. Tfos dews ii pathophysiology report. Ocul Surf. 2017;15:438–510.

24. Baudouin C, Aragona P, Messmer EM, Tomlinson A, Calonge M, Boboridis KG, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. Ocul Surf. 2013;11:246–58. https://doi.org/10.1016/j.jtos.2013.07.003.

25. Prinz J, Maffulli N, Fuest M, Walter P, Bell A, Migliorini F. Efficacy of topical administration of corticosteroids for the management of dry eye disease: systematic review and meta-analysis. Life. 2022;12:1932.

26. Pflugfelder SC, de Paiva CS. The pathophysiology of dry eye disease: what we know and future directions for research. Ophthalmology. 2017;124:S4-s13. https://doi.org/10.1016/j.ophtha.2017.07.010.

27. Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. Arch Ophthalmol. 2012;130:90–100.

28. Ryu KJ, Kim S, Kim MK, Paik HJ, Kim DH. Short-term therapeutic effects of topical corticosteroids on refractory dry eye disease: clinical usefulness of matrix metalloproteinase 9 testing as a response prediction marker. Clin Ophthalmol. 2021. https://doi.org/10.2147/OPTH.S300047.

29. Huang D, Li Z. Multidimensional immunotherapy for dry eye disease: current status and future directions. Front Ophthalmol. 2024. https://doi.org/10.3389/fopht.2024.1449283.

30. Favre H, Lahoti S, Issa N, Johnson DA, Kheirkhah A. Topical steroids in management of dry eye disease. Curr Ophthalmol Rep. 2020;8:195–200. https://doi.org/10.1007/s40135-020-00249-7.

31. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. N Engl J Med. 2005;353:1711–23.

32. De Paiva CS, Corrales RM, Villarreal AL, Farley WJ, Li D-Q, Stern ME, et al. Corticosteroid and doxycycline suppress MMP-9 and inflammatory cytokine expression, MAPK activation in the corneal epithelium in experimental dry eye. Exp Eye Res. 2006;83:526–35.

33. De Paiva CS, Corrales RM, Villarreal AL, Farley W, Li D-Q, Stern ME, et al. Apical corneal barrier disruption in experimental murine dry eye is abrogated by methylprednisolone and doxycycline. Invest Ophthalmol Vis Sci. 2006;47:2847–56.

34. Lekhanont K, Leyngold IM, Suwan-Apichon O, Rangsin R, Chuck RS. Comparison of topical dry eye medications for the treatment of keratoconjunctivitis sicca in a botulinum toxin B-induced mouse model. Cornea. 2007;26:84–9.

35. Sheppard JD, Torkildsen GL, Lonsdale JD, D'Ambrosio FA Jr, McLaurin EB, Eiferman RA, et al. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. Ophthalmology. 2014;121:475–83.

36. Byun Y-j, Kim T-i, Kwon SM, Seo KY, Kim SW, Kim EK, et al. Efficacy of combined 0.05% cyclosporine and 1% methylprednisolone treatment for chronic dry eye. Cornea. 2012;31:509–13.

37. Drzyzga Ł, Śpiewak D, Dorecka M, Wyględowska-Promieńska D. Available therapeutic options for corneal neovascularization: a review. Int J Mol Sci. 2024;25:5479.

38. Comstock TL, Decory HH. Advances in corticosteroid therapy for ocular inflammation: loteprednol etabonate. Int J Inflam. 2012;2012:789623. https://doi.org/10.1155/2012/789623.

39. McGhee CN, Watson DG, Midgley JM, Noble MJ, Dutton GN, Fern AI. Penetration of synthetic corticosteroids into human aqueous humour. Eye (Lond). 1990;4(Pt 3):526–30. https://doi.org/10.1038/eye.1990.70.

40. McGhee CN, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids: benefits and risks. Drug Saf. 2002;25:33–55. https://doi.org/10.2165/00002018-200225010-00004.

41. Mulki L, Foster CS. Difluprednate for inflammatory eye disorders. Drugs Today (Barc). 2011;47:327–33. https://doi.org/10.1358/dot.2011.47.5.1590791.

42. Jamal KN, Callanan DG. The role of difluprednate ophthalmic emulsion in clinical practice. Clin Ophthalmol. 2009;3:381–90. https://doi.org/10.2147/opth.s4460.

43. Novack GD, Howes J, Crockett RS, Sherwood MB. Change in intraocular pressure during long-term

use of loteprednol etabonate. J Glaucoma. 1998;7:266–9.

44. Łazicka-Gałecka M, Gałecki T, Szaflik JP. Safety and efficacy of loteprednol etabonate in treatment of ocular inflammatory diseases. Klinika Oczna/Acta Ophthalmologica Polonica. 2017;119:239–44. https://doi.org/10.5114/ko.2017.76217.

45. Pavesio CE, Decory HH. Treatment of ocular inflammatory conditions with loteprednol etabonate. Br J Ophthalmol. 2008;92:455–9. https://doi.org/10.1136/bjo.2007.132621.

46. Fong R, Cavet ME, DeCory HH, Vittitow JL. Loteprednol etabonate (submicron) ophthalmic gel 0.38% dosed three times daily following cataract surgery: integrated analysis of two Phase III clinical studies. Clin Ophthalmol. 2019. https://doi.org/10.2147/opth.s210597.

47. Kersey JP, Broadway DC. Corticosteroid-induced glaucoma: a review of the literature. Eye (Lond). 2006;20:407–16. https://doi.org/10.1038/sj.eye.6701895.

48. Richman JB, Tang-Liu DD. A corneal perfusion device for estimating ocular bioavailability in vitro. J Pharm Sci. 1990;79:153–7. https://doi.org/10.1002/jps.2600790215.

49. Wallsh J, Sharareh B, Gallemore R. Therapeutic effect of dexamethasone implant in retinal vein occlusions resistant to anti-VEGF therapy. Clin Ophthalmol **2016**, 947–954.

50. Rezar-Dreindl S, Eibenberger K, Pollreisz A, Bühl W, Georgopoulos M, Krall C, et al. Effect of intravitreal dexamethasone implant on intra-ocular cytokines and chemokines in eyes with retinal vein occlusion. Acta Ophthalmol. 2017;95:e119–27.

51. Starr MR, Maguire LJ, Salomão DR. Bilateral corneal deposits 1 week after starting oral prednisone therapy. JAMA Ophthalmol. 2018;136:591–2.

52. Donnenfeld ED. Difluprednate for the prevention of ocular inflammation postsurgery: an update. Clin Ophthalmol **2011**, 811–816.

53. Tajika T, Waki M, Tsuzuki M, Kida T, Sakaki H. Pharmacokinetic features of difluprednate ophthalmic emulsion in rabbits as determined by glucocorticoid receptor-binding bioassay. J Ocul Pharmacol Ther. 2011;27:29–34.

54. Amer R, Pillar S. Review on the use of difluprednate in inflammatory eye disorders: the topical steroid that goes the distance. Ocul Immunol Inflamm. 2025;33:670–82. https://doi.org/10.1080/09273948.2024.2423869.

55. Avunduk AM, Avunduk MC, Varnell ED, Kaufman HE. The comparison of efficacies of topical corticosteroids and nonsteroidal anti-inflammatory drops on dry eye patients: a clinical and immunocytochemical study. Am J Ophthalmol. 2003;136:593–602.

56. Lee HK, Ryu IH, Seo KY, Hong S, Kim HC, Kim EK. Topical 0.1% prednisolone lowers nerve growth factor expression in keratoconjunctivitis sicca patients. Ophthalmology. 2006;113:198–205. https://doi.org/10.1016/j.ophtha.2005.09.033.

57. Pflugfelder SC, Maskin SL, Anderson B, Chodosh J, Holland EJ, De Paiva CS, et al. A randomized, double-masked, placebo-controlled, multicenter comparison of loteprednol etabonate ophthalmic suspension, 0.5%, and placebo for treatment of keratoconjunctivitis sicca in patients with delayed tear clearance. Am J Ophthalmol. 2004;138:444–57.

58. Pinto-Fraga J, López-Miguel A, González-García MJ, Fernández I, López-de-la-Rosa A, Enríquez-de-Salamanca A, et al. Topical fluorometholone protects the ocular surface of dry eye patients from desiccating stress: a randomized controlled clinical trial. Ophthalmology. 2016;123:141–53.

59. Mason L, Jafri S, Dortonne I, Sheppard JD Jr. Emerging therapies for dry eye disease. Expert Opin Emerg Drugs. 2021;26:401–13.

60. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo C-K, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15:276–83.

61. McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne. Aust Ophthalmol. 1998;105:1114–9.

62. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol. 2003;136:318–26.

63. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. Arch Ophthalmol. 2000;118:1264–8.

64. Lin P-Y, Tsai S-Y, Cheng C-Y, Liu J-H, Chou P, Hsu W-M. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. Ophthalmology. 2003;110:1096–101.

65. Comstock TL, Paterno MR, Singh A, Erb T, Davis E. Safety and efficacy of loteprednol etabonate ophthalmic ointment 0.5% for the treatment of inflammation and pain following cataract surgery. Clin Ophthalmol. 2011;5:177–86. https://doi.org/10.2147/opth.S16832.

66. Jacobs R, Tran U, Chen H, Kassim A, Engelhardt B, Greer J, et al. Prevalence and risk factors associated

with development of ocular GVHD defined by NIH consensus criteria. Bone Marrow Transplant. 2012;47:1470–3.

67. Cursiefen C, Wenkel H, Martus P, Langenbucher A, Nguyen NX, Seitz B, et al. Impact of short-term versus long-term topical steroids on corneal neovascularization after non-high-risk keratoplasty. Graefes Arch Clin Exp Ophthalmol. 2001;239:514–21.

68. de Paiva CS, Pflugfelder SC. Rationale for anti-inflammatory therapy in dry eye syndrome. Arq Bras Oftalmol. 2008;71:89–95. https://doi.org/10.1590/s0004-27492008000700017.

69. Kallab M, Szegedi S, Hommer N, Stegmann H, Kaya S, Werkmeister RM, et al. Topical low dose preservative-free hydrocortisone reduces signs and symptoms in patients with chronic dry eye: a randomized clinical trial. Adv Ther. 2020;37:329–41.

70. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9:30. https://doi.org/10.1186/1710-1492-9-30.

71. Baker EH. Is there a safe and effective way to wean patients off long-term glucocorticoids? Br J Clin Pharmacol. 2020. https://doi.org/10.1111/bcp.14679.

72. Priya G, Laway BA, Ayyagari M, Gupta M, Bhat GHK, Dutta D. The glucocorticoid taper: a primer for the clinicians. Indian J Endocrinol Metab. 2024;28:350–62. https://doi.org/10.4103/ijem.ijem_410_23.

73. Flach AJ. Corneal melts associated with topically applied nonsteroidal anti-inflammatory drugs. Trans Am Ophthalmol Soc. 2001;99:205–10.

74. Ling J, Chan BC-L, Tsang MS-M, Gao X, Leung PC, Lam CW-K, et al. Current advances in mechanisms and treatment of dry eye disease: toward anti-inflammatory and immunomodulatory therapy and traditional Chinese medicine. Front Med Lausanne. 2022. https://doi.org/10.3389/fmed.2021.815075.

75. Rigas B, Huang W, Honkanen R. NSAID-induced corneal melt: clinical importance, pathogenesis, and risk mitigation. Surv Ophthalmol. 2020;65:1–11. https://doi.org/10.1016/j.survophthal.2019.07.001.

76. de Paiva CS, Pflugfelder SC, Ng SM, Akpek EK. Topical cyclosporine A therapy for dry eye syndrome. Cochrane Database Syst Rev. 2019;9:Cd010051. https://doi.org/10.1002/14651858.CD010051.pub2.

77. Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. Arch Ophthalmol. 2012;130:90–100. https://doi.org/10.1001/archophthalmol.2011.364.

78. Gao D, Da Z, Yang K, Shi Y. Comparison of seven cyclosporine A formulations for dry eye disease: a systematic review and network meta-analysis. Front Pharmacol. 2022;13:882803. https://doi.org/10.3389/fphar.2022.882803.

79. Kim EC, Choi J-S, Joo C-K. A comparison of vitamin a and cyclosporine a 0.05% eye drops for treatment of dry eye syndrome. Am J Ophthalmol. 2009;147:206-213. e203.

80. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. Ophthalmology. 2000;107:631–9. https://doi.org/10.1016/s0161-6420(99)00176-1.

81. Doctor MB, Kate A, Tallapelly HG, Basu S. The role of topical cyclosporine A in ocular surface inflammatory disorders. Semin Ophthalmol. 2025. https://doi.org/10.1080/08820538.2025.2512759.

82. Dastjerdi MH, Hamrah P, Dana R. High-frequency topical cyclosporine 0.05% in the treatment of severe dry eye refractory to twice-daily regimen. Cornea. 2009;28:1091–6.

83. Gire AI, Karakus S, Ingrodi SM, Akpek EK. Frequent dosing of topical cyclosporine A for severe ocular surface disease. J Ocul Pharmacol Ther. 2016;32:150–4.

84. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The cyclosporin A phase 2 study group. Ophthalmology. 2000;107:967–74. https://doi.org/10.1016/s0161-6420(00)00035-x.

85. Jee D, Han SY, Kim HS, Kim EC. Comparison of effects of cyclosporine 0.05% and 0.1% in dry eye with Sjögren's syndrome. BMC Ophthalmol. 2025;25:369. https://doi.org/10.1186/s12886-025-04173-x.

86. Sheppard JD, Scoper SV, Samudre S. Topical loteprednol pretreatment reduces cyclosporine stinging in chronic dry eye disease. J Ocul Pharmacol Ther. 2011;27:23–7. https://doi.org/10.1089/jop.2010.0085.

87. Othman TM, Mousa A, Gikandi PW, AbdelMabod M, Abdelrahman AM. Efficacy and safety of using topical cyclosporine A for treatment of moderate to severe dry eye disease. Saudi J Ophthalmol. 2018;32:217–21.

88. Wirta DL, Torkildsen GL, Moreira HR, Lonsdale JD, Ciolino JB, Jentsch G, et al. A clinical phase II study to assess efficacy, safety, and tolerability of water-free cyclosporine formulation for treatment of dry eye disease. Ophthalmology. 2019;126:792–800. https://doi.org/10.1016/j.ophtha.2019.01.024.

89. Rouimi F, Bouillot A, Baudouin C, Labbé A. Topical cyclosporine A and risk of ocular surface neoplasia. J Fr Ophtalmol. 2018;41:122–8. https://doi.org/10.1016/j.jfo.2017.09.005.

90. Shoughy SS. Topical tacrolimus in anterior segment inflammatory disorders. Eye Vis. 2017;4:7.

91. Liu S, Zhao Y, Ma J, Shen Z, Hu B, Peng R, et al. Efficacy evaluation of 0.05% cyclosporine A and 0.1% tacrolimus eye drops in the treatment of severe dry eye associated with chronic graft-versus-host disease. *[Zhonghua yan ke za Zhi]*. Chin J Ophthalmol. 2023;59:805–13.

92. Moawad P, Shamma R, Hassanein D, Ragab G, El Zawahry O. Evaluation of the effect of topical tacrolimus 0.03% versus cyclosporine 0.05% in the treatment of dry eye secondary to Sjogren syndrome. Eur J Ophthalmol. 2022;32:673–9.

93. Barot RK, Shitole SC, Bhagat N, Patil D, Sawant P, Patil K. Therapeutic effect of 0.1% tacrolimus eye ointment in allergic ocular diseases. J Clin Diagn Res. 2016;10:NC05.

94. Chen X, Wu J, Lin X, Wu X, Yu X, Wang B, et al. Tacrolimus loaded cationic liposomes for dry eye treatment. Front Pharmacol. 2022. https://doi.org/10.3389/fphar.2022.838168.

95. Dirar QS, Musalem HM, Al-Hazzaa SA, Al Zoba AA, Almalki AA. Effect of pegylated interferon and mitomycin C on ocular surface squamous neoplasia in xeroderma pigmentosum: a case series. Am J Case Rep. 2020;21:e921301-921301.

96. Shah A, Espana EM, Singh AD. Ocular surface squamous neoplasia associated with atopic keratoconjunctivitis. Ocul Oncol Pathol. 2017;3:22–7. https://doi.org/10.1159/000448220.

97. Pournaras JA, Chamot L, Uffer S, Zografos L. Conjunctival intraepithelial neoplasia in a patient treated with tacrolimus after liver transplantation. Cornea. 2007;26:1261–2. https://doi.org/10.1097/ICO.0b013e31813e0bed.

98. LEO Pharma A/S. Protopic® (tacrolimus) Ointment 0.03% and 0.1%. Summary of Product Characteristics (SmPC) (EU Product Information). Available online: Accessed 5 Jan 2026.

99. Shrestha E, Banstola L, Maharjan IM, Gurung B, Gurung H, Adhikari HB, et al. Assessing profile and treatment outcome in patients of ocular surface squamous neoplasia (OSSN). Nepal J Ophthalmol. 2019;11:181–8.

100. Pflugfelder SC, Stern M, Zhang S, Shojaei A. LFA-1/ICAM-1 interaction as a therapeutic target in dry eye disease. J Ocul Pharmacol Ther. 2017;33:5–12.

101. Keating GM. Lifitegrast ophthalmic solution 5%: a review in dry eye disease. Drugs. 2017;77:201–8.

102. Chan CC, Prokopich CL. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: overview of clinical trial program. J Pharm Pharm Sci. 2019;22:49–56.

103. Haber SL, Benson V, Buckway CJ, Gonzales JM, Romanet D, Scholes B. Lifitegrast: a novel drug for patients with dry eye disease. Therapeutic Adv Ophthalmol. 2019;11:2515841419870366.

104. Li J-X, Tsai Y-Y, Lai C-T, Li Y-L, Wu Y-H, Chiang C-C. Lifitegrast ophthalmic solution 5% is a safe and efficient eyedrop for dry eye disease: a systematic review and meta-analysis. J Clin Med. 2022;11:5014.

105. Holland EJ, Luchs J, Karpecki PM, Nichols KK, Jackson MA, Sall K, et al. Lifitegrast for the treatment of dry eye disease: results of a phase III, randomized, double-masked, placebo-controlled trial (OPUS-3). Ophthalmology. 2017;124:53–60.

106. Tong AY, Passi SF, Gupta PK. Clinical outcomes of lifitegrast 5% ophthalmic solution in the treatment of dry eye disease. Eye Contact Lens: Sci Clin Pract. 2020;46:S20–4.

107. Sobolewska B, Doycheva D, Deuter C, Pfeffer I, Schaller M, Zierhut M. Treatment of ocular rosacea with once-daily low-dose doxycycline. Cornea. 2014;33:257–60. https://doi.org/10.1097/ico.0000000000000051.

108 Onghanseng N, Ng S, Halim MS, Nguyen Q. Oral antibiotics for chronic blepharitis. Cochrane Database Syst Rev. 2021. https://doi.org/10.1002/14651858.CD013697.pub2.

109. Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2011;52:2050–64. https://doi.org/10.1167/iovs.10-6997g.

110. Satitpitakul V, Ratanawongphaibul K, Kasetsuwan N, Reinprayoon U. Efficacy of azithromycin 1.5% eyedrops vs oral doxycycline in meibomian gland dysfunction: a randomized trial. Graefes

Arch Clin Exp Ophthalmol. 2019;257:1289–94. https://doi.org/10.1007/s00417-019-04322-1.

111. Upaphong P, Tangmonkongvoragul C, Phinyo P. Pulsed oral azithromycin vs 6-week oral doxycycline for moderate to severe Meibomian Gland Dysfunction: a randomized clinical trial. JAMA Ophthalmol. 2023;141:423–9. https://doi.org/10.1001/jamaophthalmol.2023.0302.

112. Yoo SE, Lee DC, Chang MH. The effect of low-dose doxycycline therapy in chronic meibomian gland dysfunction. Korean J Ophthalmol. 2005;19:258–63. https://doi.org/10.3341/kjo.2005.19.4.258.

113. Kagkelaris KA, Makri OE, Georgakopoulos CD, Panayiotakopoulos GD. An eye for azithromycin: review of the literature. Ther Adv Ophthalmol. 2018;10:2515841418783622. https://doi.org/10.1177/2515841418783622.

114. Kashkouli MB, Fazel AJ, Kiavash V, Nojomi M, Ghiasian L. Oral azithromycin versus doxycycline in meibomian gland dysfunction: a randomised double-masked open-label clinical trial. Br J Ophthalmol. 2015;99:199–204. https://doi.org/10.1136/bjophthalmol-2014-305410.

115. Ben Ephraim Noyman D, Chan CC, Mimouni M, Safir M. Systemic antibiotic treatment for meibomian gland dysfunction-a systematic review and meta-analysis. Acta Ophthalmol. 2024;102:e1–10. https://doi.org/10.1111/aos.15681.

116. Macsai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis). Trans Am Ophthalmol Soc. 2008;106:336–56.

117. Asbell PA, Maguire MG, Pistilli M, Ying GS, Szczotka-Flynn LB, Hardten DR, et al. N-3 fatty acid supplementation for the treatment of dry eye disease. N Engl J Med. 2018;378:1681–90. https://doi.org/10.1056/NEJMoa1709691.

118. Aragona P, Rolando M. Towards a dynamic customised therapy for ocular surface dysfunctions. Br J Ophthalmol. 2013;97:955–60. https://doi.org/10.1136/bjophthalmol-2012-302568.

119. Aragona P, Giannaccare G, Dammino E, D'Esposito F, Genovese P, Postorino EI, et al. Observational clinical investigation evaluating an ophthalmic solution containing Xanthan Gum and low concentration Desonide Phosphate in dry eye disease treatment. Ophthalmol Ther. 2024;13:2559–73. https://doi.org/10.1007/s40123-024-01003-z.

120. Fogagnolo P, Giannaccare G, Mencucci R, Villani E, Orfeo V, Aragona P. Effectiveness of a new active tear substitute containing 0.2% hyaluronic acid and 0.001% hydrocortisone on signs and symptoms of dry eye disease by means of low- and high-tech assessments. Ophthalmol Ther. 2024;13:251–66. https://doi.org/10.1007/s40123-023-00833-7.

121. Rodriguez-Pomar C, Carpena-Torres C, Serramito M, Perez-de-Lara MJ, Martinez-Aguila A, Martin-Gil A, et al. Decreased inflammatory biomarkers after using artificial tears with *Aloe vera* and hypromellose for dry eye. Clin Exp Optom. 2025. https://doi.org/10.1080/08164622.2025.2485236.

122. Downie LE, Rumney N, Gad A, Keller PR, Purslow C, Vingrys AJ. Comparing self-reported optometric dry eye clinical practices in Australia and the United Kingdom: is there scope for practice improvement? Ophthalmic Physiol Opt. 2016;36:140–51.

123. Williamson JF, Huynh K, Weaver MA, Davis RM. Perceptions of dry eye disease management in current clinical practice. Eye Contact Lens: Sci Clin Pract. 2014;40:111–5.

124. Xue AL, Downie LE, Ormonde SE, Craig JP. A comparison of the self-reported dry eye practices of New Zealand optometrists and ophthalmologists. Ophthalmic Physiol Opt. 2017;37:191–201.

125. Downie LE, Keller PR, Vingrys AJ. An evidence-based analysis of Australian optometrists' dry eye practices. Optom Vis Sci. 2013;90:1385–95.

126. Jones L, Craig JP, Markoulli M, Karpecki P, Akpek EK, Basu S, et al. TFOS DEWS III management and therapy report. Am J Ophthalmol. 2025. https://doi.org/10.1016/j.ajo.2025.05.039.

127. Wolffsohn JS, Semp DA, Dutta D, Jones L, Craig JP. Clinical practice patterns in the management of dry eye disease: a TFOS international survey 2023-24. Ocul Surf. 2025;36:164–72. https://doi.org/10.1016/j.jtos.2024.12.008.

128. Sheppard J, Shen Lee B, Periman LM. Dry eye disease: identification and therapeutic strategies for primary care clinicians and clinical specialists. Ann Med. 2023;55:241–52.

129. Mondal H, Kim H-J, Mohanto N, Jee J-P. A review on dry eye disease treatment: recent progress, diagnostics, and future perspectives. Pharmaceutics. 2023;15:990.

130. Bitton E, Lacroix Z, Léger S. In-vivo heat retention comparison of eyelid warming masks. Contact Lens Anterior Eye. 2016;39:311–5.

131. Borchman D. The optimum temperature for the heat therapy for meibomian gland dysfunction. Ocul Surf. 2019;17:360–4.

132. Giannaccare G, Pellegrini M, Scalzo GC, Borselli M, Ceravolo D, Scorcia V. Low-level light therapy

versus intense pulsed light for the treatment of meibomian gland dysfunction: preliminary results from a prospective randomized comparative study. Cornea. 2023;42:141–4.

133. Xue AL, Wang MT, Ormonde SE, Craig JP. Randomised double-masked placebo-controlled trial of the cumulative treatment efficacy profile of intense pulsed light therapy for meibomian gland dysfunction. Ocul Surf. 2020;18:286–97.

134. Sy A, O'Brien KS, Liu MP, Cuddapah PA, Acharya NR, Lietman TM, et al. Expert opinion in the management of aqueous Deficient Dry Eye Disease (DED). BMC Ophthalmol. 2015;15:133.

135. Qian W, Wu Y, Liu X, Liu Y, Li M, Zhao T, et al. Efficacy of 0.05% cyclosporine A on tear inflammatory cytokines and goblet cell function after corneal refractive surgery. J Ophthalmic Inflamm Infect. 2025;15:36. https://doi.org/10.1186/s12348-025-00462-0.

136. Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74:1983–9.

137. Michaelov E, McKenna C, Ibrahim P, Nayeni M, Dang A, Mather R. Sjögren's syndrome associated dry eye: impact on daily living and adherence to therapy. J Clin Med. 2022. https://doi.org/10.3390/jcm11102809.

138. Jonsson R, Vogelsang P, Volchenkov R, Espinosa A, Wahren-Herlenius M, Appel S. The complexity of Sjögren's syndrome: novel aspects on pathogenesis. Immunol Lett. 2011;141:1–9.

139. Pflugfelder SC, Huang AJ, Feuer W, Chuchovski PT, Pereira IC, Tseng SC. Conjunctival cytologiec features of primary Sjögren's syndrome. Ophthalmology. 1990;97:985–91.

140. Johnson ME. The association between symptoms of discomfort and signs in dry eye. Ocul Surf. 2009;7:199–211.

141. Miljanović B, Dana R, Sullivan DA, Schaumberg DA. Impact of dry eye syndrome on vision-related quality of life. Am J Ophthalmol. 2007;143:409-415. e402.

142. Ahmed F, Burt J, Roland M. Measuring patient experience: concepts and methods. Patient Patient-Centered Outcomes Res. 2014;7:235–41.

143. Valdés-Arias D, Locatelli EVT, Sepulveda-Beltran PA, Mangwani-Mordani S, Navia JC, Galor A. Recent United States developments in the pharmacological treatment of dry eye disease. Drugs. 2024;84:549–63. https://doi.org/10.1007/s40265-024-02031-6.

144. Flts A, Medina R, Akpek EK. The evolution of cyclosporine treatments for treatment of ocular surface diseases. Curr Opin Allergy Clin Immunol. 2024;24:360–7. https://doi.org/10.1097/aci.0000000000001017.

145. Shan H, Liu W, Li Y, Pang K. The autoimmune rheumatic disease related dry eye and its association with retinopathy. Biomolecules. 2023. https://doi.org/10.3390/biom13050724.

146. Kılıççıoğlu A, Oncel D, Celebi ARC. Autoimmune disease-related dry eye diseases and their placement under the revised classification systems: an update. Cureus. 2023;15:e50276. https://doi.org/10.7759/cureus.50276.

147. Promelle V, Goeb V, Gueudry J. Rheumatoid arthritis associated episcleritis and scleritis: an update on treatment perspectives. J Clin Med. 2021. https://doi.org/10.3390/jcm10102118.

148. Lamba N, Lee S, Chaudhry H, Foster C. A review of the ocular manifestations of rheumatoid arthritis. Cogent Med. 2016. https://doi.org/10.1080/2331205X.2016.1243771.

149. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. Arthritis Rheum. 2008;58:15–25.

150. Dammacco R. Systemic lupus erythematosus and ocular involvement: an overview. Clin Exp Med. 2018;18:135–49.

151. El-Shereef RR, Mohamed AS, Hamdy L. Ocular manifestation of systemic lupus erythematosus. Rheumatol Int. 2013;33:1637–42.

152. Tseng CH, Tai YH, Hong CT, Dai YX, Chen TJ, Cherng YG, et al. Systemic lupus erythematosus and risk of dry eye disease and corneal surface damage: a population-based cohort study. Int J Environ Res Public Health. 2023. https://doi.org/10.3390/ijerph20053776.

153. Murugan SB, Somanath A. Commentary: systemic lupus erythematosus retinopathy: eye or multisystem involvement? Indian J Ophthalmol. 2023;71:1994–5. https://doi.org/10.4103/IJO.IJO_3386_22.

154. Musa M, Chukwuyem E, Ojo OM, Topah EK, Spadea L, Salati C, et al. Unveiling ocular manifestations in systemic Lupus Erythematosus. J Clin Med. 2024. https://doi.org/10.3390/jcm13041047.

155. De Paiva C, Chotikavanich S, Pangelinan S, Pitcher J, Fang B, Zheng X, et al. IL-17 disrupts corneal

barrier following desiccating stress. Mucosal Immunol. 2009;2:243–53.

156. Garcia-Posadas L, Hodges R, Li D, Shatos M, Storr-Paulsen T, Diebold Y, et al. Interaction of IFN-γ with cholinergic agonists to modulate rat and human goblet cell function. Mucosal Immunol. 2016;9:206–17.

157. Wieczorek R, Jakobiec FA, Sacks EH, Knowles DM. The immunoarchitecture of the normal human lacrimal gland: relevancy for understanding pathologic conditions. Ophthalmology. 1988;95:100–9.

158. Pflugfelder SC, Stern ME. Biological functions of tear film. Exp Eye Res. 2020;197:108115. https://doi.org/10.1016/j.exer.2020.108115.

159. Leonardi A, Van Setten G, Amrane M, Ismail D, Garrigue JS, Figueiredo FC, et al. Efficacy and safety of 0.1% cyclosporine A cationic emulsion in the treatment of severe dry eye disease: a multicenter randomized trial. Eur J Ophthalmol. 2016;26:287–96. https://doi.org/10.5301/ejo.5000779.

160. Hoy SM. Ciclosporin ophthalmic emulsion 0.1%: a review in severe dry eye disease. Drugs. 2017;77:1909–16. https://doi.org/10.1007/s40265-017-0834-x.

161. Geerling G, Hamada S, Trocmé S, Ræder S, Chen X, Fassari C, et al. Real-world effectiveness, tolerability and safety of cyclosporine A 0.1% cationic emulsion in severe keratitis and dry eye treatment. Ophthalmol Ther. 2022;11:1101–17. https://doi.org/10.1007/s40123-022-00487-x.

162. Labetoulle M, Leonardi A, Pisella PJ, Baudouin C. Ciclosporin A cationic emulsion 0.1% for the management of dry eye disease: facts that matter for eye-care providers. Ocul Immunol Inflamm. 2023;31:1707–15. https://doi.org/10.1080/09273948.2022.2088566.

163. Sheppard JD, Nichols KK. Dry eye disease associated with Meibomian gland dysfunction: focus on tear film characteristics and the therapeutic landscape. Ophthalmol Ther. 2023;12:1397–418. https://doi.org/10.1007/s40123-023-00669-1.