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REVIEW

Recent advances in drug treatments for dry eye disease

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ABSTRACT

Introduction: Dry eye disease (DED) is a common ocular condition with a significant impact on patients' quality of life. Conventional treatments include behavioral changes, tear substitutes, and anti-inflammatory agents; however, recent advances in the understanding of DED pathogenesis have opened the way to the development of novel treatment strategies able to target several pathways involved in the onset and persistence of DED.

Areas covered: Literature search was conducted on PubMed and Scopus around the term 'dry eye disease' and others involving its pathophysiology and therapeutic strategy. The primary focus was on recent drugs approved by FDA or under investigation in phase 3 clinical trials. Google and ClinicalTrials.gov were used for obtaining information about the status of FDA approval and ongoing clinical trials.

Expert opinion: Due to its multifaced pathogenesis, DED management is often challenging, and patients' needs are frequently unmet. Recently, several novel treatments have been either FDA-approved or studied in late-phase trials. These novel drugs target-specific biological components of the ocular surface and reduce inflammation and ocular pain. Additionally, new drug delivery systems allow for increased bioavailability, improve effective dosing, and minimize ocular side effects. These advances in drug therapies show real promise for better management of DED patients.

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Dry eye; treatment; DED; eye drops; RCT; randomized clinical trials

1. Introduction

Dry eye disease (DED) is a very common eye disease, with a prevalence, according to estimates, from 5% to 50% [1,2]. The tear film plays a fundamental role in maintaining the optical surface and a clear vision, and DED can negatively impact vision and ocular comfort, influencing patient's daily activities and quality of life [3].

Several factors contribute to the development of DED, including eye disorders such as blepharitis and meibomian gland dysfunction (MGD), as well as several systemic diseases such as diabetes mellitus, Sjogren syndrome (SS), rheumatoid arthritis, and systemic lupus erythematosus [4]. DED has been traditionally classified into aqueous deficient and evaporative, both of which can determine tear hyperosmolarity [5]. However, the mechanisms underlying the disease are often interconnected, resulting in a mixed pathogenesis. Wetting defects and hyperosmolar stress can exacerbate friction and chronic mechanical irritation on the ocular surface, setting off a cascade of inflammatory events and superficial damage [6]. Immune responses further complicate the picture, contributing to the production of inflammatory mediators that disrupt the integrity of the corneal and conjunctival epithelium. This, in turn, sensitizes the corneal nerve endings and amplifies the recruitment and migration of inflammatory cells, perpetuating the chronic vicious cycle of dry eye.

[5–7]. Over the past few years, improved understanding of DED pathogenesis, as well as technological improvements in drug delivery systems, has led to the development of novel therapies able to target DED signs and symptoms. Identifying the dominant mechanisms involved in the perpetuation of the dry eye vicious cycle for each patient plays a key role in the selection of an appropriate treatment.

The aim of this review is to delineate DED pathophysiology and current treatment options and to underline the recent advances in DED drug treatments, by highlighting the most recent FDA-approved drugs and drugs in the DED development pipeline which are currently in the last stage of clinical research (phase 3).

2. Materials and methods

A search on the PubMed and Scopus medical databases was carried out. Database search strategy was formulated around the term 'dry eye disease', 'treatment,' and several other terms regarding its pathophysiology and therapeutic strategy ('vicious circle,' 'inflammation,' 'tear substitute,' etc.). The focus of the research was the most recent DED drug therapies and phase 3 clinical trials. Additional Google search was conducted to gain information on FDA-approved DED treatments and on ClinicalTrials.gov for ongoing clinical trials. After selection of DED drugs, the search was repeated with the term 'dry eye' and each drug name (formulation, brand name, and/or clinical trial name). The search terms were selected after

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Article highlights

- Dry eye disease (DED) is a very common eye condition that severely impacts patients' quality of both vision and life.
- Advances in our understanding of DED pathophysiology have shed a light into multiple novel pathways involved in the onset and persistence of the disease.
- Novel therapeutic targets have been identified, and a strong research interest has been put in the development of novel treatment strategies for DED, as confirmed by the number of new drugs either recently approved or under late phases of clinical research.
- Novel drug delivery systems allow for greater drug bioavailability and show promises for reducing eye drops instillations, thus contributing to improving DED management and increasing patients' quality of life.

considering the available literature and/or gathered from linked bibliographies. Duplicate and unrelated papers were excluded. Bibliographies from the initial searches were also manually searched for additional inclusions (Figure 1).

3. DED pathophysiology

The main components of the tear film are lipids, water, electrolytes, proteins, and mucins, all essential for lubrication, hydration, and protection against infections and injury [8]. Each component is secreted by specific ocular surface structures, and dysfunction of this integrated unit may develop as a result of aging, decrease in supportive factors, blink abnormalities, systemic inflammatory diseases, ocular surface diseases, surgeries that disrupt the trigeminal afferent sensory nerves, and conditions that modify the efferent cholinergic nerves needed to stimulate tear secretion [9].

A key component of DED is tear hyperosmolarity, resulting from several mechanisms [6]. All forms of DED can be grossly divided into predominantly evaporative dry eye, where hyperosmolarity mainly results from a deficient lipid layer in MGD and excessive tear evaporation, and predominantly aqueous deficient dry eye, where hyperosmolarity mainly occurs due to an inadequate rate of tear secretion. These two forms frequently overlap, and environmental factors can trigger the onset of DED or cause worsening of the condition [10].

Several studies on animal models and humans showed that hyperosmolar stress on the ocular surface initiates an immune response by activating mitogen-activated protein kinases (MAPKs), stimulating the secretion of pro-inflammatory cytokines (e.g. interleukin [IL]-1b, TNF-a, and IL-6); chemokines, and matrix metalloproteinases (MMP-3 and MMP-9); and inducing epithelial cell apoptosis [11]. This, in turn, exposes and irritates the nociceptive receptors leading to pain and discomfort and alters the optical properties of the tear film, leading to visual disturbances [12].

4. Management

Principles of DED management begin with control of external conditions, by avoiding dry atmospheres and high airspeeds (e.g. fans, car heaters and air conditioning) and being aware of the blinking rate in several activities (e.g. reading, computer work, or using digital devices) [13]. First-line treatments are usually preservative-free artificial tears (ATs). Tear substitutes attempt to improve lubrication and decrease evaporation, leading to temporary symptom relief with few side effects [14]. A wide variety of tears substitutes are available as non-prescription products, including solutions, sprays, gels, and ointments [15]. The DED distinction in the predominantly evaporative and predominantly aqueous deficient forms helps in their management [16]. For meibomian gland dysfunction, daily lid hygiene, warm compresses, hypoallergic cleansing products, and gentle massage to express the lipid oils are indicated [17]. Topical antibiotics, low-dose glucocorticoids, and combinations of the two agents can also be used for short-term treatment and, if not sufficient, oral tetracyclines can be used. Antibiotics may have therapeutic effects

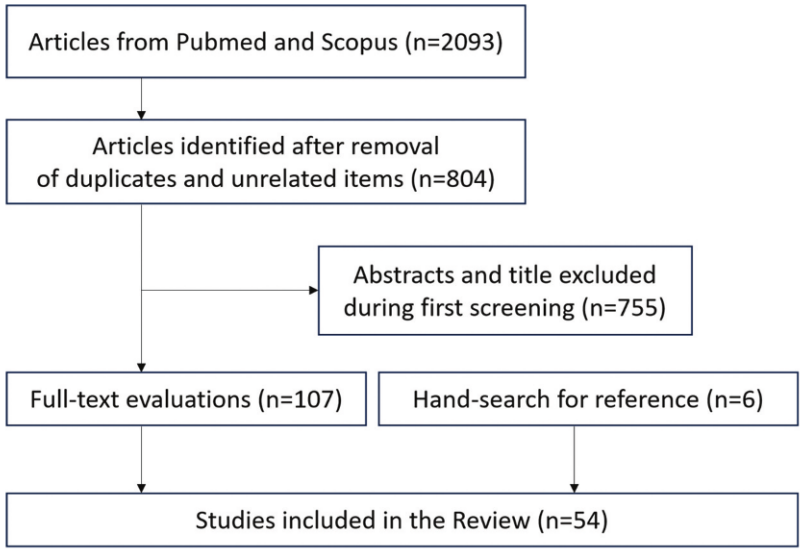

Figure 1. Details of the literature search and study selection processes.

through anti-inflammatory mechanisms rather than through, or in addition to, their antibacterial properties [18].

In the case of persistence of DED signs and symptoms despite the reduction of predisposing risk factors, full adherence to tear substitutes and eyelid therapy are necessary; sometimes, antibiotics, anti-inflammatory agents, or punctal plugs may be required for a better control of the disease [15]. Ophthalmic corticosteroids decrease inflammation and may be used on a short-term basis for moderate to severe DED. Several studies showed clinical benefit of topical steroid such as loteprednol, methylprednisolone, or fluorometholone, administration for several weeks to 1 month [19]. Punctal plugs are placed to occlude tear-duct drainage in aqueous tear-deficient DED [9]. Other second-line treatments include anti-inflammatory agents such as cyclosporine 0.05% ophthalmic emulsion. Education on proper usage and monitoring for eye infection should be performed [17]. If signs and/or symptoms persist, topical corticosteroids for longer durations, autologous serum (AS) eye drops, contact lenses, amniotic membrane grafts, or surgical punctal closure can all be considered [17,20]. Lastly, increasing dietary intake of omega-3 fatty acids or taking an omega-3 fatty acid supplement was shown to have some clinical benefit in patients with DED [21].

5. Recent advances in DED treatment

Despite the above-mentioned treatment strategies, a large proportion of DED patients still present signs and symptoms and, over the past few years, the development of novel treatment strategies has gained growing interest.

Several new DED drugs have recently been FDA-approved, becoming part of the DED treatment armamentarium, while many others have gone through several steps of their developmental process and are currently in phase 3 clinical research.

Table 1–3 summarize the recent advances in drug treatments for DED.

6. FDA-approved DED drugs

6.1. Lifitegrast

Lifitegrast is a small-molecule integrin antagonist that exerts its anti-inflammatory effects by mimicking ICAM-1 and effectively inhibiting the interaction between ICAM-1 and LFA-1 involved in multiple aspects of lymphocyte activation and migration. Lifitegrast 5% (Xiidra®; Novartis, Basel, Switzerland) was FDA-approved in 2016 for the treatment of DED [52].

Several clinical trials demonstrated the efficacy of lifitegrast 5% in treating DED signs and symptoms [22,53–55]. The phase 3 trial OPUS-3 (NCT02284516) showed that lifitegrast significantly improved Eye Dryness Score (EDS) compared to placebo in a large population of patients affected by aqueous-deficient dry eye (ADDE) at 14, 42, and 84 days (always $p < 0.001$) [22]. Ocular adverse events (AEs) were mild to moderate and mainly represented by transient ocular irritation and ocular hyperemia, while non-ocular AEs included dysgeusia, headaches, erythema, and musculoskeletal pain. Similar results on AEs were reached by the SONATA study (NCT01636206), which was specifically designed to examine the long-term safety profile of lifitegrast over a 1-year period [23]. Most common AEs were irritation at the instillation site (burning), instillation site reaction, reduction in visual acuity, dry eye, and dysgeusia. No safety concerns were raised [23].

6.2. KPI-121

Loteprednol etabonate ophthalmic suspension 0.25%, also known as KPI-121 0.25% (EYSUVIS®; Kala Pharmaceuticals, Arlington, Massachusetts, USA) was FDA-approved in 2020 for the short-term treatment (up to 2 weeks) of signs and symptoms of DED.

Loteprednol etabonate (LE) is a corticosteroid that was retro-metabolically engineered to minimize corticosteroid-related adverse effects, such as increase in intraocular pressure (IOP) and cataract formation [56].

KPI-121 was developed utilizing a novel drug delivery technology based on mucus-penetrating particles (MPPs) that allows to overcome the mucus barrier and enhance the LE penetration into the ocular surface target tissues [57]. The development of KPI-121 0.25% for DED involved one phase 2 trial (NCT02188160) and three phase 3 trials: STRIDE 1 (NCT02813265), STRIDE 2 (NCT02819284), and STRIDE 3 (NCT03616899), with a total enrollment of over 2800 patients. The first two multicenter, double-masked, randomized studies showed improvements in Ocular Discomfort Score (ODS) and conjunctival hyperemia compared to vehicle after 2 weeks ($p < 0.05$ and $p < 0.001$, respectively), with main reported side effect being pain at the site of instillation (6.1 to 9.7%) [24,58,59]. The 0.25% concentration was chosen based on the better pharmacokinetic profile of the MPP system compared to the conventional LE 0.5% [58].

[24,57,58,60,61] Currently, short-term use of KPI-121 0.25% is indicated to treat DED flares, potentially breaking the vicious cycle of inflammation. In addition, the use of KPI-121 0.25% may be indicated as an induction treatment in patients on other chronic immunomodulatory DED treatments, before the clinical efficacy of the new therapeutic agent begins, potentially, to optimize the ocular surface before cataract or refractive surgery, and to treat DED flares after surgery [58].

6.3. Cyclosporin A

Cyclosporin A (CsA) is a targeted immunomodulator with the ability to reduce the activation of T-cells and the infiltration of T-lymphocytes into the lacrimal glands. Additionally, it inhibits the ocular surface epithelial cell apoptosis [62–65]. CsA has proven to be an effective treatment for DED by increasing tear production, reducing the release of inflammatory cytokines, and protecting conjunctival epithelial cells [66]. Unfortunately, the high CsA hydrophobicity required cyclosporin to be dissolved in oil-based emulsions that are scarcely tolerated and have a short ocular surface retention time and subsequent low bioavailability [67]. A CsA ophthalmic emulsion of 0.05% (anionic oil-in-waternote) (Restasis®; Allergan, Irvine, California, USA) was FDA-approved for DED treatment in 2002. More recently,

Table 1. Recent FDA-approved drug treatments for dry eye disease (DED). Data are reported as follows, unless stated otherwise: numerical values for the results and adverse events columns refer to the end of the study follow-up; mean changes are calculated from baseline; the time of treatment for each study group is identical to the follow-up time.

FDA approved						
Therapy	Features	Study Design	Participants	Results	AEs	GRADE QoE
Lifitegrast 5% approved in 2016	– Integrin antagonist – Blocks lymphocyte activation and migration	Holland et al. (OPUS-3) [22] *Design* Phase 3 RCT (NCT02284516) multicenter (41 sites) double-masked placebo-controlled *Randomization* 1:1 stratified by baseline ICSS score (≤1.5 or > 1.5) and EDS (<60 or ≥ 60) *Follow-up* 84 days	*Disease* ADDE *Participants* 711 adults *Groups* 356 Placebo 355 Lifitegrast 5.0% *twice daily*	*Mean changes in EDS* Lifitegrast > Placebo TE, 7.16; 95% CI, 3.04–11.28 ($p = 0.0007$) *Mean changes in ODS* No changes at all timepoints ($p > 0.05$)	*Participants with ≥ 1 TEAE* 87 (24.6%) Placebo 172 (48.2%) Lifitegrast No correlated serious TEAEs.	⊕ ⊕ ⊕ ⊕ high
		Donnenfeld et al. (SONATA) [23] *Design* Phase 3 RCT (NCT01636206) multicenter (22 sites) double-masked placebo-controlled *Randomization* 2:1, based on web response system *Follow-up* 360 days	*Disease* ADDE *Participants* 331 adults *Groups* 220 Lifitegrast 5.0% 111 Placebo *twice daily*	The main outcomes regarded AEs	*Participants with ≥ 1 TEAE* 53.6% Lifitegrast 34.2% Placebo No correlated serious TEAEs. *Most common TEAEs* irritation at the instillation site (burning), instillation site reaction, reduction in visual acuity, dry eye and dysgeusia	⊕ ⊕ ⊕ ⊕ high
Loteprednol etabonate 0.25% (KPI-121 0.25%) approved in 2020	- Corticosteroid with minimal corticosteroid-related adverse effects	Holland et al. 2020 (NCT02188160, STRIDE 1) [24] *Design* Phase 2 RCT NCT02188160 Phase 3 RCT NCT02813265 multicenter double-masked vehicle-controlled *Randomization* 1:1 *Follow-up* 15 days	*Participants* 1065 adults *Groups* 532 KPI-121 0.25% 533 Vehicle *4 times daily*	*Mean changes in ODS* *Phase 2:* KPI-121 better than vehicle ($p < 0.0489$) *Phase 3:* KPI-121 better than vehicle ($p < 0.0001$) *Change in conjunctival hyperemia* *Phase 2:* KPI-121 better than vehicle ($p < 0.009$) *Phase 3:* KPI-121 better than vehicle ($p < 0.0001$)	*Most common TEAEs* Instillation site pain 6.1–9.7% KPI-121 6.1–10.3%Vehicle *Change in IOP* No significant differences ($p > 0.05$)	⊕ ⊕ ⊕ ⊕ high
CsA ophthalmic solution 0.09% (OTX-101) approved in 2019	– Calcineurin inhibitor – Nanomicellar solution	Sheppard et al. 2019 *Design* Phase 2b/3 RCT NCT02188160 Phase 3 RCT NCT02813265 multicenter double-masked vehicle-controlled *Randomization* 1:1 *Follow-up* 84 days	*Participants* 1048 adults *Groups* 524 OTX-101 0.09% 524 Vehicle *Twice daily*	*Increase in STS ≥10 mm* 16.6% OTX-101 9.0% Vehicle ($p < 0.0001$) *Mean STS* 14.6 ± 9.9 mm OTX-101 12.8 ± 9.2 mm Vehicle ($p < 0.0001$) *Mean change in global SANDE score* −29.0% OTX-101 −30.4% Vehicle ($p = 0.3539$)	*Participants with ≥ 1 TEAE* 203 (38.7%) OTX-101 142 (27.1%) Vehicle No correlated serious TEAEs.	⊕ ⊕ ⊕ ⊕ high
CsA ophthalmic solution 0.1% (CyclASol 0.1%) approved in 2023	– Calcineurin inhibitor - Nonaqueous solution without water, surfactants, oil or preservatives	Wirta et al. [25] *Design* Phase 2 RCT NCT02617667 multicenter double-masked vehicle-controlled *Randomization* 1:1:1:1 stratified based on total CFS score and VAS symptom dryness *Follow-up* 16 weeks	*Participants* 207 adults *Groups* 51 CyclASol 0.05% 51 CyclASol 0.1% 52 Vehicle 53 Restasis *Twice daily*	*Mean change in CFS* *Week 4:* −1.92 ± 2.108 CyclASol 0.05% −1.88 ± 2.046 CyclASol 0.1% vs −0.85 ± 2.476 Restasis ($p = 0.0104$, $p = 0.0100$, respectively) *Mean change in CLGS* *Week 12:* −0.82 ± 1.438 CyclASol 0.05% −0.24 ± 1.238 Vehicle ($p = 0.0223$) *Changes in dryness symptoms (VAS)* No significant changes compared to vehicle ($p > 0.05$) *Mean change in OSDI* CyclASol 0.1% > vehicle ($p < 0.001$)	*Participants with ≥ 1 TEAE* 18 (35.5%) CyclASol 0.05% 12 (23.5%) CyclASol 0.1% 14 (26.9%) Vehicle 21 (39.6%) Restasis Mild to moderate. 3 serious ocular TEAEs reported, at least possibly related to treatment. *Most common TEAEs* Visual acuity reduction	⊕ ⊕ ⊕ ⊕ high
		Sheppard et al. 2021 (ESSENCE) [26] *Design* Phase 2b/3 RCT NCT03292809 multicenter (9 sites) double-masked vehicle-controlled *Randomization* 1:1, stratified by OSDI score *Follow-up* 12 weeks	*Pathogenesis:* ADDE *Participants* 328 adults *Groups* 162 CyclASol 0.1% 166 Vehicle *Twice daily*	*Mean change in CFS* *Week 4:* CyclASol > Vehicle −0.8 (95% CI, −1.3 to −0.4); $p = 0.0002$ *Mean change in CLGS* *Week 4:* CyclASol > Vehicle −0.6 (95% CI, −0.9 to −0.3); $p = 0.0003$ *Mean change in OSDI* *Week 4:* No significant differences ($p = 0.2634$)	*N/A*	⊕ ⊕ ⊕ ⊕ high

(*Continued*)

Table 1. (Continued).

Therapy	Features	Study Design	Participants	Results	AEs	GRADE QoE
FDA approved						
Varenicline solution nasal spray approved in 2021	- Nicotinic acetylcholine (nACh) receptor agonist - Activates the parasympathetic trigeminal nerve pathway (TPP)	Wirta et al. 2022 (ONSET-1) [27]				
		Design Phase 2b NCT03636061 multicenter double-masked vehicle-controlled *Randomization* 1:1:1:1 no stratification by baseline factors *Follow-up* 28 days	*Participants* 182 adults *Groups* 43 Vehicle 47 OC-01 0.006 mg 48 OC-01 0.03 mg 44 OC-01 0.06 mg *Twice daily*	*LS mean change in STS* 7.7 mm (95% CI, 3.8–11.7) OC-01 0.03 mg ($p < 0.001$ vs vehicle) 7.5 mm (95% CI, 3.4–11.6) OC-01 0.06 mg ($p < 0.001$ vs vehicle) *LS mean change in EDS* −13.3 (95% CI, −25.0 to − 1.7) OC-01 0.03 mg ($p = 0.021$ vs vehicle) −9.8; (95% CI, −21.8 to 2.2) OC-01 0.06 mg ($p = 0.13$ vs vehicle)	*Participants with ≥ 1 TEAE* 11 (26%) Vehicle 33 (70%) OC-01 0.006 mg 44 (92%) OC-01 0.03 mg 41 (93%) OC-01 0.06 mg No correlated severe TEAEs *Most common TEAEs:* Sneezing, dose-dependent increases in cough and throat irritation	⊕ ⊕ ⊕ ○ moderate
		Wirta et al. 2022 (ONSET-2) [28]				
		Design Phase 3 NCT03873246 multicenter (22 sites) double-masked vehicle-controlled *Randomization* 1:1:1 block randomization, stratification based on anesthetized STS (≤5 mm or >5 mm), EDS (<60 or ≥ 60), and study site *Follow-up* 4 weeks	*Participants* 758 adults *Groups* 260 OC-01 0.03 mg 246 OC-01 0.06 mg 252 Vehicle *Twice daily*	*Anesthetized STS improvement ≥10 mm* 47.3% OC-01 0.03 mg 49.2% OC-01 0.06 mg 27.8% Vehicle (always $p < 0.0001$ vs vehicle) *LS mean change in anesthetized STS* +11.3 mm OC-01 0.03 mg +11.5 mm OC-01 0.06 mg +6.3 mm Vehicle (always $p < 0.0001$ vs vehicle) *LS mean change in EDS* −10.3 mm OC-01 0.03 mg −9.0 mm OC-01 0.06 mg −7.4 mm Vehicle (always $p > 0.05$ vs vehicle)	*Participants with ≥ 1 TEAE* *both ocular and non-ocular* 253 (97.3%) OC-01 0.03 mg 243 (99.2%) OC-01 0.06 mg 143 (57.0%) Vehicle No correlated severe TEAEs *Most common TEAEs:* *Non ocular* Sneezing, cough, throat irritation, instillation site irritation, nasopharyngitis *Ocular* Conjunctival hyperemia, Reduced visual acuity	⊕ ⊕ ⊕ ⊕ high
		Quiroz-Mercado et al. 2022 (MYSTIC) [29]				
		Design Phase 2 NCT03873246 single site double-masked vehicle-controlled *Randomization* 1:1:1, using a block size of 6 using the online program, Sealed Envelope *Follow-up* 84 days	*Participants* 123 adults *Groups* 41 OC-01 0.03 mg 41 OC-01 0.06 mg 41 Vehicle *Twice daily*	*Anesthetized STS improvement ≥10 mm* 36.6% OC-01 0.03 mg ($p > 0.05$ vs vehicle) 48.8% OC-01 0.06 mg ($p = 0.02$ vs vehicle) 24.4% Vehicle *LS mean change in anesthetized STS* +10.8 mm OC-01 0.03 mg +11.0 mm OC-01 0.06 mg +6.0 mm Vehicle (always $p < 0.01$ vs vehicle)	*Participants with ≥ 1 TEAE* *both ocular and non-ocular* 10 (24.4%) OC-01 0.03 mg 10 (24.4%) OC-01 0.06 mg 12 (29.3%) Vehicle No correlated severe TEAEs	⊕ ⊕ ⊕ ○ moderate
NOV03 approved in 2023	- Perfluorohexyloctane which might replace the lipid layer of the tear film, preventing evaporation of the latter – Unknown mechanism of action	Tauber et al. 2022 (GOBI)				
		Design Phase 3 NCT04139798 multicenter (26 sites) double-masked saline-controlled *Randomization* 1:1, stratified by baseline EDS *Follow-up* 8 weeks	*Pathogenesis:* Evaporative DED *Participants* 597 adults *Groups* 303 NOV03 294 Saline solution 0.6% *4 times daily*	*Mean change in CFS (NEI score)* −2.0 NOV03 −1.0 Saline ($p < 0.001$) *Mean change in EDS (VAS)* −27.4 NOV03 −19.7 Saline ($p < 0.001$)	*Participants with ≥ 1 TEAE* 29 (9.6%) NOV03 22 (7.5%) Saline No correlated serious TEAEs.	⊕ ⊕ ⊕ ⊕ high
		Sheppard et al. 2022 (MOJAVE)				
		Design Phase 3 NCT04567329 multicenter (42 sites) double-masked saline-controlled *Randomization* 1:1, stratified by baseline EDS *Follow-up* 8 weeks	*Pathogenesis:* Evaporative DED *Participants* 597 adults *Groups* 311 NOV03 309 Saline solution 0.6% *4 times daily*	*Mean change in CFS score (NEI score)* −2.3 NOV03 −1.1 Saline ($p < 0.001$) *Mean change in EDS (VAS)* −29.5 NOV03 −19.0 Saline ($p < 0.001$)	*Participants with ≥ 1 TEAE* 40 (12.9%) NOV03 38 (12.3%) Saline No correlated serious TEAEs.	⊕ ⊕ ⊕ ⊕ high

QoE = quality of evidence; RCT = randomized clinical trial; ICSS = inferior corneal staining score; EDS = eye dryness score; ADDE = aqueous-deficient dry eye; TE = treatment effect; CI = confidence intervals; ODS = ocular discomfort score; TEAE = treatment-emergent adverse events; IOP = intraocular pressure; SANDE = Symptom Assessment iN Dry Eye; CFS = corneal fluorescein staining; VAS = Visual analog scale; OSDI = ocular surface disease index; LS = least square; STS = Schirmer Test Score; NEI = National Eye Institute; STS = Schirmer test score; CLGS = conjunctival lissamine green staining.

innovative drug delivery systems have been used to develop novel CsA formulations with the aim of causing less ocular irritation and offering better adherence and longer retention time. Two of these CsA formulations have recently been approved.

6.3.1. OTX-101

OTX-101 (CEQUA™ Sun Pharmaceutical Industries, Cranbury, New Jersey, U.S.A.) is an innovative 0.09% cyclosporine nanomicellar solution that has received FDA approval in 2019 for enhancing tear production in individuals diagnosed

Table 2. Dry eye disease (DED) drugs in phase 3 clinical trials. Data are reported as follows: unless stated otherwise: numerical values for the results and adverse events columns refer to the end of the study follow-up; mean changes are calculated from baseline; the time of treatment for each study group is identical to the follow-up time.

Phase 3 Clinical Trials						
Therapy	Features	Study Design	Participants	Results	AEs	GRADE QoE
Anti-inflammatory and/or immunosuppressive						
CsA 0.05% ophthalmic gel (CyclAGel 0.05%)	– Calcineurin inhibitor – A carbomer is used as vehicle			Peng et al. 2021 [30]		
		Design Phase 2 RCT (NCT02284516) multicenter (13 sites) double-masked positive-controlled *Randomization* 1:1:1:1 *Follow-up* 12 weeks	*Participants* 240 adults *Groups* 59 CyclAGel 0.05%/QD 60 CyclAGel 0.05%/BID 60 CyclAGel 0.1%/QD 61 Restasis control/BID	*Mean change in EDS (VAS)* −29.17 ± 23.77 CyclAGel 0.05%/QD −32.07 ± 21.77 CyclAGel 0.05%/BID −29.75 ± 19.72 CyclAGel 0.1%/QD −27.26 ± 24.95 Restasis control/BID ($p = 0.7841$)	*Participants with ≥ 1 TEAE* 14 (23%) CyclAGel 0.05%/QD 17 (29%) CyclAGel 0.05%/BID 15 (25%) CyclAGel 0.1%/QD 16 (27%) Restasis control/BID ($p = 0.8828$)	⊕ ⊕ ○ ○ low
				Peng et al. 2021 (COSMO) [31]		
		Design Phase 3 RCT (NCT04541888) multicenter (37 sites) double-masked positive-controlled *Randomization* 1:1 block randomization *Follow-up* 84 days	*Participants* 627 adults *Groups* 315 CyclAGel 0.05% 312 Vehicle *Once nightly*	*ICSS improvement ≥ 1 point* 232 (73.7%) CyclAGel 0.05% 166 (3.2%) Vehicle ($p < 0.0001$) *STS values* 4.1 ± 6.71 CyclAGel 0.05% 2.7 ± 5.34 Vehicle ($p < 0.05$) *Mean change in EDS* −29 CyclAGel 0.05% −31Vehicle ($p > 0.05$)	*Participants with ≥ 1 TEAE* 127 (39.6%) CyclAGel 0.05% 96 (30.6%) Vehicle *Most common TEAEs* eye pain, eye foreign body sensation, vision loss, and urinary tract infection	⊕ ⊕ ⊕ ⊕ high
CsA 0.1% cationic emulsion (CE) EMA approved in 2015	– Calcineurin inhibitor – Cationic emulsion			Leonardi et al. 2016 (SANSIKA) [32]		
		Design Phase 3 RCT NVG10E117 Multicenter (50 sites) double-masked vehicle-controlled *Randomization* 2:1 *Follow-up* 6 months + 6 months open-label	*Participants* 261 adults *Groups* 154 CsA CE 91 Vehicle *Once daily*	*Mean change in CFS* CsA CE > Vehicle ($p = 0.017$) *Mean change in OSDI* −13.6 CsA CE −14.1 Vehicle ($p = 0.858$) *Mean HLA-DR AUF* 49917 CsA CE 76062 Vehicle ($p = 0.021$)	*Participants with ≥ 1 TEAE* 37.0% CsA CE 21.1% Vehicle *Most common TEAEs* Instillation site pain 29.2% CsA CE 8.9% Vehicle	⊕ ⊕ ⊕ ⊕ high
				Baudouin et al. 2017 (SICCANOVE) [33]		
		Design Phase 3 RCT NVG10E117 Multicenter (50 sites) double-masked vehicle-controlled *Randomization* 1:1 *Follow-up* 6 months	489 adults *Groups* 241 CsA CE 248 Vehicle *Once daily*	*Mean change in CFS* −1.05 CsA CE −0.82 Vehicle ($p = 0.009$) *Mean changes in VAS score* −12.8 CsA CE −11.2 Vehicle ($p = 0.808$) Stinging/burning improved significantly more than in the vehicle group; $p = 0.038$ *Mean changes in HLA-DR AUF* −21875 CsA CE −1334 Vehicle ($p < 0.05$)	*Participants with ≥ 1 TEAE* 56 (23.1%) CsA CE 72 (28.8%) Vehicle	⊕ ⊕ ⊕ ⊕ high
Cenegermin	- Recombinant human nerve growth factor (rh-NGF)			Sacchetti et al. 2019		
		Design Phase 2a RCT NCT02188160 single site open label multiple-dose *Randomization* 1:1 *Follow-up* 4 weeks	*Participants* 40 adults *Groups* 20 rhNGF 20 µg/ml 20 rhNGF 4 µg/ml *Twice daily*	*Mean changes in OSDI* −22.9 rhNGF 20 µg/ml ($p < 0.001$) −16.7 rhNGF 4 µg/ml ($p = 0.0035$) *Mean changes in CFS* −5.6 rhNGF 20 µg/ml ($p < 0.001$) −2.9 rhNGF 4 µg/ml ($p < 0.001$) *Mean changes in CLGS* −3.9 rhNGF 20 µg/ml ($p < 0.001$) −2.3 rhNGF 4 µg/ml ($p < 0.001$) *Mean changes in STS* +5.3 rhNGF 20 µg/ml ($p = 0.0006$) +3.0 rhNGF 4 µg/ml ($p = 0.0734$)	*Participants with ≥ 1 TEAE* 14 rhNGF 20 µg/ml 15 rhNGF 4 µg/ml All mild to moderate.	⊕ ⊕ ○ ○ low
Tanfanercept 0.25% ophthalmic solution	- TNF receptor 1 (TNFR1) which blocks TNF pathway			Dong et al. 2022 [34]		
		Design Phase 2 RCT NCT04092907 single site double-masked placebo-controlled *Randomization* 1:1 *Follow-up* 8 weeks	*Disease:* Moderate to severe DED *Participants* 100 adults *Groups* 50 Tanfanercept 0.25% 50 Placebo *Twice daily* *All groups were exposed to CAE model*	*LS Mean change in ICSS* −0.61 ± 0.11 Tanfanercept −0.54 ± 0.11 Placebo ($p = 0.65$) *Mean change in STS* +1.87 ± 0.62 Tanfanercept +1.28 ± 0.62 Placebo ($p = 0.50$)	*Participants with ≥ 1 TEAE* 7 (14.0%) Tanfanercept 4 (8.0%) Placebo Mild to moderate. *Most common TEAEs* Conjunctivitis, conjunctival redness	⊕ ⊕ ⊕ ○ moderate
Thymosin β4 (Tβ4)	- Naturally occurring G-actin-binding protein			Sosne et al. [35]		
		Design Phase 2 RCT NCT01393132 single site double-masked placebo-controlled *Randomization* 1:1 *Follow-up* 28 days	*Disease:* Moderate to severe DED *Participants* 72 adults *Groups* 36 Tβ4 0.1% 36 placebo *Twice daily* *Both groups were exposed to CAE model*	*Mean change in CCSS post-CAE* −0.37 Tβ4 0.1% +0.16 Placebo ($p = 0.0075$) *Mean change in OD4SQ post-CAE* +1.6 Tβ4 0.1% +2.2 Placebo ($p = 0.0244$)	*Participants with ≥ 1 TEAE* 2 (5.6%) Tβ4 5 (13.9%) Placebo Mild to moderate.	⊕ ⊕ ⊕ ○ moderate

(*Continued*)

Table 2. (Continued).

Therapy	Features	Study Design	Participants	Results	AEs	GRADE QoE
Phase 3 Clinical Trials						
Anti-inflammatory and/or immunosuppressive						
EBI-005 (Isunakinra)	- Chimera protein that blocks IL-1 pathway	Goldstein et al. 2016				
		Design Phase 1b/2a NCT01745887 multicenter (8 sites) double-masked vehicle-controlled *Randomization* 30:22:22 *Follow-up* 6 weeks	*Disease:* Moderate to severe DED *Participants* 74 adults *Groups* 30 Isunakinra 5 mg/ml 22 Isunakinra 20 mg/ml 22 Vehicle *Thrice daily*	*Mean change in OSDI* −18.9 Isunakinra −19.0 Vehicle ($p > 0.05$) *Mean change in CFS* −3.0 Isunakinra −2.7 Vehicle ($p > 0.05$)	*Participants with ≥ 1 TEAE* 12 (27%) Isunakinra 8 (27%) Vehicle No correlated severe TEAEs *Most common TEAEs:* Blood glucose increased (3), eye pain (2), upper respiratory tract infection (2)	⊕ ⊕ ⊕ ○ moderate
Reproxalap	- Binds to reactive aldehyde species (RAPS), blocking proinflammatory signaling cascades	Clark et al. 2021 [36]				
		Design Phase 2a NCT03162783 single site double-masked *Randomization* 1:1:1 *Follow-up* 29 days	*Participants* 51 adults *Groups* 17 reproxalap 0.5% 17 reproxalap 0.1% 17 reproxalap 0.5% (lipid) *4 times daily*	*Mean change in OD4SQ* p < 0.05 reproxalap 0.5% p > 0.05 reproxalap 0.1% p > 0.05 reproxalap 0.5% (lipid) *Mean change in OSDI* p > 0.05 in all groups *Tear levels of Malondialdehyde (MDA)* $P = 0.009$ reduction across all groups	*Participants with ≥ 1 TEAE* 100% reproxalap 0.5% 8 (47%) reproxalap 0.1% 100% reproxalap 0.5% (lipid) *Most common TEAEs* Ocular discomfort, transient pain upon instillation	⊕ ⊕ ○ ○ low
		Clark et al. 2021 [37]				
		Design Phase 2b NCT04567329 multicenter double-masked vehicle-controlled *Randomization* 1:1:1 *Follow-up* 12 weeks	*Participants* 300 adults *Groups* 100 reproxalap 0.1% 100 reproxalap 0.25% 100 vehicle *4 times daily*	*Mean change in OD4SQ dryness* −0.6 reproxalap 0.1% −0.5 reproxalap 0.25% −0.9 vehicle ($p = 0.047$ for 0.25% vs vehicle) *Mean change in OSDI* −5.9 reproxalap 0.1% −7.2 reproxalap 0.25% −5.3 vehicle *Mean change in STS* +2.2 reproxalap 0.1% +3.0 reproxalap 0.25% +1.3 vehicle *Mean change in ICFS* −0.2 reproxalap 0.1% −0.2 reproxalap 0.25% −0.1 vehicle *Mean change in CLGS* −0.2 reproxalap 0.1% −0.3 reproxalap 0.25% −0.2 vehicle	*Participants with ≥ 1 TEAE* 50% reproxalap 0.1% 94% reproxalap 0.25% 31% vehicle No severe correlated TEAEs *Most common TEAEs* Ocular discomfort, transient mild pain upon instillation	⊕ ⊕ ⊕ ○ moderate
TOP1630	- Narrow-spectrum kinase inhibitor (NSKI)	Taylor et al. 2019 [38]				
		Design Phase 2 NCT03088605 single site double-masked saline-controlled *Randomization* 1:1 *Follow-up* 29 days	*Participants* 61 adults *Groups* 31 TOP1630 30 Placebo *3 times daily*	*Mean change in ODS* −1.3 TOP1630 −1.4 Placebo ($p = 0.02$) *Mean change in CLGS* −0.7 ± 3.99 TOP1630 +1.1 ± 3.28 Placebo ($p = 0.06$)	*Participants with ≥ 1 TEAE* 6 (19.4%) TOP1630 6 (20.0%) Placebo No severe TEAEs	⊕ ⊕ ⊕ ○ moderate
ALY688 (ADP-355)	– Adiponectin receptor pathway activator	Sall et al. 2023 [39]				
		Design Phase 1/2a NCT04201574 single site double-masked vehicle-controlled *Randomization* 1:1:1 *Follow-up* 8 weeks	*Disease:* Moderate to severe DED *Participants* 138 adults *Groups* 46 ALY688 0.1% 46 ALY688 0.4% 46 Vehicle *Twice daily*	*EDS* ALY688 0.4% < vehicle (−7.27; $p = 0.067$) *Mean change in CLGS* −1.68 ± 3.38 ALY688 0.4% −0.34 ± 2.29 Vehicle ($p = 0.043$) *Mean change in CFS* −2.90 ± 2.34 ALY688 0.4% −2.00 ± 2.25Vehicle ($p = 0.079$)	*Participants with ≥ 1 TEAE* 6 (19.4%) TOP1630 6 (20.0%) Placebo No severe TEAEs	⊕ ⊕ ⊕ ○ moderate
Secretagogues						
Diquafosol sodium 3% Approved in Japan (2010) and other Asian Countries	– P2Y2 purinergic receptor agonist	Takamura et al. [40]				
		Design Phase 3 NCT01240382 multicenter (49 sites) double-masked vehicle-controlled *Randomization* 1:1 *Follow-up* 4 weeks	*Participants* 286 adults *Groups* 144 diquafosol 3% 143 sodium hyaluronate *6 times daily*	*Mean change in CFS* −2.12 ± 0.14 diquafosol 3% −2.08 ± 0.13 sodium hyaluronate 0.1% ($p > 0.05$) *Mean change in Rose Bengal staining* −3.06 ± 0.19 diquafosol 3% −2.38 ± 0.18 sodium hyaluronate 0.1% ($p = 0.010$)	*Participants with ≥ 1 TEAE* 26.4% diquafosol 3% 18.9% sodium hyaluronate No severe TEAEs *Most common TEAEs* Eye irritation	⊕ ⊕ ⊕ ○ moderate
Rebamipide 2% (OPC-12759)	– Quinolinone derivative	Kinoshita et al. 2012 [41]				
		Design Phase 3 NCT00885079 multicenter investigator-masked active-controlled *Randomization* 1:1 stratification based on Sjögren's syndrome and CFS *Follow-up* 4 weeks	*Participants* 188 adults *Groups* 93 diquafosol 3% 95 sodium hyaluronate *4/6 times daily*	*Mean change in CFS* −3.7 diquafosol 3% −2.9 sodium hyaluronate 0.1% ($p < 0.01$) *Mean change in CLGS* −4.5 ± 0.3 diquafosol 3% −2.4 ± 0.3 sodium hyaluronate 0.1% ($p < 0.001$) *Mean change in STS* +0.5 ± 0.2 diquafosol 3% +1.0 ± 0.3 sodium hyaluronate 0.1% ($p = 0.229$)	*Participants with ≥ 1 TEAE* 27 (29.0%) diquafosol 3% 19 (20.0%) sodium hyaluronate No severe TEAEs *Most common TEAEs* Dysgeusia (9.7%), possibly caused by the bitter taste associated with the active ingredient	⊕ ⊕ ⊕ ⊕ high

(*Continued*)

Table 2. (Continued).

Phase 3 Clinical Trials						
Therapy	Features	Study Design	Participants	Results	AEs	GRADE QoE
Anti-inflammatory and/or immunosuppressive						
Tavilermide (MIM-D3)	– Synthetic neurotrophin mimetic acting as a TrkA receptor agonist			Meerovitch et al. 2013 [42]		
		Design Phase 2 NCT01257607 multicenter (2 sites) double-masked placebo-controlled *Randomization* 1:1:1 *Follow-up* 28 days	*Participants* 150 adults *Groups* 50 MIM-D3 1% 50 MIM-D3 5% 50 Placebo *Twice daily* *All groups were exposed to CAE model*	*Mean change in CFS post-CAE* +1.44 ± 1.67 MIM-D3 1% +1.66 ± 1.51 MIM-D3 5% +2.18 ± 1.59 placebo (always $p < 0.05$ compared to placebo) *Mean change in CLGS post-CAE* MIM-D3 1% significantly lower than placebo at day 14 and 28 ($p < 0.05$) *LS Mean change in ocular dryness* −2.16 MIM-D3 5% −2.40 placebo ($p = 0.034$)	*Participants with ≥ 1 TEAE* 15 (30.0%) MIM-D3 1% 23 (46.0%) MIM-D3 5% 18 (36.0%) Placebo No severe correlated TEAEs	⊕ ⊕ ⊕ ○ moderate
				Antioxidant agents		
Visomitin (SkQ1)	– Novel synthetic antioxidant			Petrov et al. 2016 [43]		
		Design Phase 2 NCT02121301 single site double-masked placebo-controlled *Randomization* 1:1:1 *Follow-up* 29 days	*Participants* 91 adults *Groups* 30 SkQ1 1.55 µg/mL 30 SkQ1 0.155 µg/mL 31 Placebo *Twice daily* *All groups were exposed to CAE model*	*Mean change in CFS post-CAE* −0.08 SkQ1 1.55 µg/mL +0.10 SkQ1 0.155 µg/mL +0.50 Placebo (1.55 µg/mL SkQ1 vs placebo; $p = 0.021$) *Mean change in CLGS post-CAE* −0.12 SkQ1 0.155 µg/mL 0.00 Placebo (0.155 µg/mL SkQ1 vs placebo; $p = 0.04$) *Mean change in OD4SQ post-CAE* +0.1 SkQ1 1.55 µg/mL −0.3 SkQ1 0.155 µg/mL +0.5 Placebo (0.155 µg/mL SkQ1 vs placebo; $p = 0.01$)	*Participants with ≥ 1 TEAE* 7 SkQ1 1.55 µg/mL 6 SkQ1 0.155 µg/mL 5 Placebo No severe correlated TEAEs	⊕ ⊕ ⊕ ○ moderate
				Channels modulators		
AR-15512	- Transient receptor potential melastatin 8 (TRPM8)			Wirta et al. 2022 (COMET-1) [44]		
		Design Phase 2b NCT04498182 multicenter (15 sites) double-masked vehicle-controlled *Randomization* 1:1:1 by interactive web response system *Follow-up* 84 days	*Participants* 369 adults *Groups* 123 AR-15512 0.0014% 123 AR-15512 0.003% 123 Vehicle *Twice daily*	*Mean change in STS (no anesthesia)* *Day 14* +15.7 AR-15512 0.0014% +19.7 AR-15512 0.003% +6.0 Vehicle (both AR-15512 vs vehicle; $p < 0.0001$) *Mean change in CLGS* −0.30 ± 0.60 AR-15512 0.003% +1.34 ± 0.60 Vehicle ($p = 0.0365$) *Mean change in ODS-VAS* −13.3 AR-15512 0.0014% −20.6 AR-15512 0.003% −13.6 Vehicle (0.003%vs vehicle; $p < 0.0001$)	*Participants with ≥ 1 TEAE* 57 (47.1%) AR-15512 0.0014% 63 (51.6%) AR-15512 0.003% 26 (20.6%) Vehicle No severe correlated TEAEs *Most common TEAEs* Instillation site burning or stinging (37.2%, 43.4% and 3.2% respectively)	⊕ ⊕ ⊕ ⊕ high
SYL1001 (Tivanisiran)	- Small interfering RNA (siRNA) targeting the human transient receptor potential vanilloid 1 (TRVP1)			Benitez-Del-Castillo et al. 2016 [45]		
		Design Phase 1 + 2 Phase 2 NCT01438281 (SYL1001_I) single site open-label NCT01776658 (SYL1001_II) NCT02455999 (SYL1001_III) multicenter double-masked placebo-controlled *Randomization* 1:1:1 (II, III) *Follow-up* 20 days	*Participants* 30 adults (I) 60 adults (II) 66 adults (III) 156 adults (total) *Groups* (I) SYL1001 2.25% *Groups* (II) Placebo SYL1001 1.125% SYL1001 2.25% *Groups* (III) Placebo SYL1001 0.375% SYL1001 0.75% *Once daily in all studies*	*Mean change in ODS-VAS* −1.73 ± 0.32 SYL1001 1.125% −0.91 ± 0.34 Placebo ($p = 0.013$) *Conjunctival hyperemia* 50% SYL1001 1.125% 20% Placebo ($p < 0.05$)	*Participants with ≥ 1 TEAE* I 15% Placebo 10% SYL1001 1.125% 0% SYL1001 2.25% No severe correlated TEAEs II 8% Placebo 0% SYL1001 0.375% 5% SYL1001 0.75% No severe correlated TEAEs	⊕ ⊕ ⊕ ⊕ high
				Blood derived products		
Autologous serum	- galenic preparation, usually at 20% concentration – presents similar composition to that of tears			Celebi et al. 2014 [46]		
		Design prospective single site double-masked *Randomization* 1:1 by random number table method *Follow-up* 1 month, washout, 1 month	*Disease* Severe DED refractory to other treatments *Participants* 20 adults (40 eyes) *Groups* 10 20% diluted AS 10 PFAT *4 times daily*	*Change in TBUT* Significantly higher in AS ($p < 0.001$) *Change in OSDI* −55.18% AS −19.50% PFAT ($p < 0.001$) *Change in STS* No statistically significant difference *Change in vital staining* No statistically significant difference	*N/A*	⊕ ⊕ ○ ○ low
Platelet rich plasma (PRP)	– Blood derived product with 2.5 times more platelets than whole blood			Avila et al. 2018 [47]		
		Design Phase 3 NCT02257957 single site controlled *Randomization* 1:1 *Follow-up* 90 days	*Disease* Severe DED due to Sjogren syndrome *Participants* 30 adults *Groups* 15 PRP *(4 times)* + HA 15 HA *5 times daily*	*Mean change in STS* +2.5 mm PRP + HA −0.2 mm HA ($p < 0.002$) *Mean change in TBUT* +2.4 sec PRP + HA −0.2 sec HA ($p = 0.005$) *Mean change in CLGS* −1.3 PRP + HA −0.2 HA ($p < 0.001$) *Mean change in OSDI* −25 PRP + HA +1 HA ($p < 0.001$)	*N/A*	⊕ ⊕ ⊕ ○ moderate

(*Continued*)

Table 2. (Continued).

Therapy	Features	Study Design	Participants	Results	AEs	GRADE QoE
Phase 3 Clinical Trials						
Anti-inflammatory and/or immunosuppressive						
Amniotic membrane derivates (AMEED)	– Amniotic membrane extract	Pérez et al. 2022 [48]				
		Design Phase 3 NCT05598242 single site *Follow-up* 4 weeks	*Disease* Severe ocular surface disease *Participants* 25 adults (36 eyes)	*VQF25 questionnaire* not statistically different ($p = 0.4657$) improvement in foreign body sensation, itching and stinging ($p < 0.05$) *Epithelization* All patients with corneal ulcer showed complete epithelization.	*N/A*	⊕ ○ ○ ○ very low
Antibiotics						
Azithromycin eye drops (AZM)	- Macrolide antibiotic with antimicrobial, anti-inflammatory, and immunomodulatory effects	Arita et al. 2021 [49]				
		Design UMIN000037715 single site single-blind active-controlled *Randomization* 1:1 *Follow-up* 2 weeks	*Disease* DED with MGD-associated posterior blepharitis *Participants* 36 adults *Groups* 16 AZM 1% eye drops 20 PFAT *Twice daily for 2 days, then once daily for 12 days*	*Mean change in SPEED score* −7.0 ± 1.1 AZM 1% −3.4 ± 0.3 PFAT ($p = 0.018$) *Mean change in Tear Osmolarity* −22 mOsm/L AZM 1% +5.7 mOsm/L PFAT ($p = 0.014$) *Mean change in Meibum grade* −1.9 ± 0.1 AZM 1% −0.6 ± 0.1 PFAT ($p < 0.001$)	*Participants with ≥ 1 TEAE* AZM 1% Eye irritation 12 (75%) Blurred vision 8 (50%) Constipation 2 (12.5%)	⊕ ⊕ ⊕ ○ moderate
		Satitpitakul et al. 2019 [50]				
		Design TCTR20140524001 single site single-masked parallel-group *Randomization* 1:1 *Follow-up* 4 weeks	*Disease* moderate to severe MGD *Participants* 169 adults *Groups* 85 AZM 1.5% eye drops *Twice daily for 2 days, then once daily* 84 oral doxycycline *Twice daily*	*Improvement in meibum expression* 68.06% AZM 1.5% 70.0% oral doxycycline *Improvement in CLGS* 40.28% AZM 1.5% 48.75% oral doxycycline *Improvement in ocular discomfort* 75.00% AZM 1.5% 78.57% oral doxycycline *Significant improvements compared to baseline ($p < 0.01$), but no significant intergroup differences (always $p < 0.05$)*	*Participants with ≥ 1 TEAE* 45 (54.88%) AZM 1.5% 16 (19.75%) oral doxycycline *Most common TEAEs* *AZM 1.5%* eye irritation (45.12%), blurred vision (13.41%) *Oral doxycycline* gastrointestinal disturb (11%)	⊕ ⊕ ⊕ ○ moderate
Oral doxycycline	– Tetracycline derivate - anti-inflammatory and lipid regulation effects	Yoo et al. 2005 [51]				
		Design TCTR20140524001 single site double-blinded parallel-group *Randomization* 1:1:1 *Follow-up* 4 weeks	*Disease* chronic MGD *Participants* 150 adults *Groups* 50 Doxycycline 200 mg 50 Doxycycline 20 mg 50 Placebo *Twice daily*	*Mean change in TBUT* +1.55 sec Doxycycline 200 mg +1.72 Doxycycline 20 mg +0.04 sec Placebo ($p = 0.992$ across doxycycline doses; $p < 0.05$ vs placebo) *Mean change in STS* +1.85 mm Doxycycline 200 mg +2.38 mm Doxycycline 20 mg −0.68 mm Placebo ($p = 0.624$ across doxycycline doses; $p < 0.05$ vs placebo)	*Participants with ≥ 1 TEAE* 18 (39.1%) Doxycycline 200 mg 8 (17.4%) Doxycycline 20 mg 3 (6.38%) Placebo *Most common TEAEs* Gastrointestinal problems (21), followed by itchy skin, urticaria, erythematous papules (7)	⊕ ⊕ ⊕ ○ moderate
Oral dietary supplementation						
Blueberry gummy	- Contains pterostilbene, which suppresses inflammation, apoptosis, and oxidative stress	Phase 3 trial registered: NCT05027087.	N/A	N/A	N/A	N/A
Omega 3 fatty acids	- Anti-inflammatory properties	Phase 3 trial on OmegaD softgels registered: NCT04181593.	N/A	N/A	N/A	N/A

QoE = quality of evidence; RCT = randomized clinical trial; ICSS = inferior corneal staining score; EDS = eye dryness score; ADDE = aqueous-deficient dry eye; TE = treatment effect; CI = confidence intervals; TEAE = treatment-emergent adverse events; CFS = corneal fluorescein staining; VAS = Visual analog scale; OSDI = ocular surface disease index; LS = least square; STS = Schirmer Test Score; NEI = National Eye Institute; AUF = arbitrary units of fluorescence; SANDE = Symptoms Assessment in Dry Eye; CAE = controlled adverse environment; TFBUT = tear film break-up time; TCSS = total corneal staining score; CCSS = central corneal staining score; OD4SQ = ocular discomfort and 4-symptom questionnaire; MGD= meibomian gland dysfunction; CLGS = conjunctival lissamine green staining; PFAT = preservative-free artificial tears; SPEED = Standardized Patient Evaluation of Eye Dryness.

with DED. In a pooled analysis of two randomized clinical trials (RCTs) (phase 2b, NCT02254265; phase 3, NCT02688556) Sheppard et al. evaluated the efficacy and safety of OTX-101 [68]. Treatment with OTX-101 0.09% twice daily demonstrated a significant improvement in the percentage of patients who obtained a Schirmer test score of ≥10 mm at 84 days compared to vehicle (16.6% vs 9.0%; $p < 0.0001$). The increase in tear production was greater in cases of higher baseline disease severity. However, mean changes in global Symptom Assessment iN Dry Eye (SANDE) score were not significantly different than vehicle (−29.0% vs −30.4%; $p = 0.3539$). The reported AEs were predominantly mild, with instillation site pain (burning and stinging) being the most frequently reported [68].

6.3.2. CyclAsol

CyclASol 0.1% (Vevye™ cyclosporine ophthalmic solution 0.1%; Novaliq GmbH, Cambridge, Massachusetts, USA) is a nonaqueous solution of CsA that does not contain water, surfactants, oils, or preservatives and was FDA approved for the treatment of DED in 2023. Although not soluble in water, CsA is soluble in water-free and preservative-free novel EyeSol technology based on semi-fluorinated alkanes. EyeSol was designed to improve ocular comfort, enhance local bioavailability, and provide an early onset of efficacy. This clear solution rapidly spread on the ocular surface without causing visual disturbances related to the use of oils and thanks to its refractive index, which is similar to the one of water. Preclinical animal experiments proved its higher corneal barrier penetration compared to Restasis® (AbbVie, North

Table 3. Summary of the significant findings ($p < 0.05$) for each randomized clinical trial described in the manuscript. *Rose Bengal was used instead of lissamine green for the evaluation of ocular surface staining. **Symptoms were evaluated with different questionnaires.

Therapy	RCT	STS	CFS	CLGS	TBUT	Osm	MG	Symptoms**
FDA Approved								
Lifitegrast 5%	Holland et al. 2017 (OPUS-3) [22]							EDS
Loteprednol etabonate 0.25% (KPI-121)	Holland et al. 2020 [24]							ODS
CsA ophthalmic solution 0.09% (OTX-101)	Sheppard et al. 2019	⊕						
CsA ophthalmic solution 0.1% (CyclASol 0.1%)	Wirta et al. 2019 [25]	⊕	⊕	⊕				OSDI
	Sheppard et al. 2021 (ESSENCE) [26]		⊕	⊕				
Varenicline solution nasal spray	Wirta et al. 2022 (ONSET-1) [27]	⊕						EDS
	Wirta et al. 2022 (ONSET-2) [28]	⊕						
	Quiroz-Mercado et al. 2022 [29]	⊕						
NOV03	Tauber et al. 2022 (GOBI)		⊕					EDS
	Sheppard et al. 2022 (MOJAVE)		⊕					EDS
Dry Eye Disease drugs in Phase 3 Clinical Trials								
Anti-inflammatory and/or immunosuppressive								
CsA 0.05% ophthalmic gel (CyclAGel 0.05%)	Peng et al. 2021 (COSMO) [31]	⊕						
CsA 0.1% cationic emulsion (CE)	Leonardi et al. 2016 (SANSIKA) [32]		⊕					
	Baudouin et al. 2017 (SICCANOVE) [33]		⊕					EDS
Tanfanercept 0.25% ophthalmic solution	Dong et al. 2022 [34]							
Thymosin β4 (Tβ4)	Sosne et al. 2015 [35]		⊕					
EBI-005 (Isunakinra)	Goldstein et al. 2016							
Reproxalap 0.25%	Clark et al. 2021 [36]	⊕						OSDI
TOP1630	Taylor et al. 2019 [38]			⊕				ODS
ALY688 (ADP-355)	Sall et al. 2023 [39]			⊕				EDS
Secretagogues								
Diquafosol sodium 3%	Takamura et al. [40]			⊕				
Rebamipide 2% (OPC-12759)	Kinoshita et al. 2012 [41]		⊕	⊕*				
Tavilermide (MIM-D3)	Meerovitch et al. 2013 [42]		⊕	⊕				
Antioxidant agents								
Visomitin (SkQ1) 1.55 µg/mL	Petrov et al. 2016 [43]		⊕					
Visomitin (SkQ1) 0.155 µg/mL				⊕				OD4SQ
Channels modulators								
AR-15512 0.0014%	Wirta et al. 2022 (COMET-1) [44]	⊕						
AR-15512 0.003%		⊕		⊕				ODS
SYL1001 1.125% (Tivanisiran)	Benitez-Del-Castillo et al. 2016 [45]							ODS
Blood derived products								
Autologous serum	Celebi et al. 2014 [46]				⊕			OSDI
Platelet rich plasma (PRP)	Avila et al. 2018 [47]	⊕		⊕	⊕			OSDI
Antibiotics								
Azithromycin eye drops 1.0%	Arita et al. 2021 [49]					⊕	⊕	SPEED
Azithromycin eye drops 1.5%	Satitpitakul et al. 2019 [50]			⊕				
Oral doxycycline 100 mg				⊕				
Oral doxycycline 200 mg	Yoo et al. 2005 [51]	⊕			⊕			
Oral doxycycline 20 mg		⊕			⊕			

STS = Schirmer test score, CFS = corneal fluorescein staining, CLGS = conjunctival lissamine green staining, TBUT = tear break-up time, Osm = tear osmolarity, MG, meibum grade, EDS = eye dryness score, ODS = ocular disease score, OSDI = ocular surface disease index, OD4SQ = ocular discomfort and 4-symptom questionnaire, SPEED = Standardized Patient Evaluation of Eye Dryness.

Chicago, Illinois, USA) and Ikervis® (Santen Pharmaceutical, Ofuka-cho Kita-ku, Osaka, Japan) [69,70]. A phase 2 clinical trial (NCT02617667) on DED patients unresponsive to ATs treatment assessed the safety, efficacy, and tolerability of two concentrations of CyclASol (0.05% and 0.1%) [25]. CyclASol demonstrated good results at both concentrations [25]: when compared directly to open-label Restasis®, CyclASol exhibited a faster onset of action, with noticeable improvements in corneal fluorescein staining (CFS) (mean difference [MD] = −1.92 CyclASol 0.05%, MD = −1.88 CyclASol 0.1%; always $p < 0.05$ vs vehicle) and conjunctival lissamine green staining (CLGS) scores (MD = −0.82 CyclASol 0.05%; $p < 0.05$ vs vehicle), as early as 2 weeks of treatment. In addition, CyclASol 0.1% trended toward a greater effect in relieving symptoms compared to the 0.05% formulation, determining a significant improvement in OSDI score over vehicles, with the highest impact on reading, driving at night, working with a computer, and watching TV. The study reported excellent safety and tolerability with a high study completion rate of 98% [25]. A phase 2b/3 clinical trial (NCT03292809) was also conducted in patients with predominantly aqueous deficient DED and confirmed the efficacy of CyclASol 0.1% in reducing both CFS (MD = −0.8; $p = 0.0002$ vs vehicle) and CLGS (MD = −0.6;

$p = 0.0003$ vs vehicle) as early as 2 weeks after treatment initiation [26]. OSDI score improved significantly at 4 weeks; however, the reduction was not statistically significant compared to vehicle [26].

6.4. Varenicline (OC-01)

Varenicline solution (OC-01) nasal spray (Tyrvaya® nasal spray 0.03 mg; Oyster Point Pharma, Princeton, New Jersey, USA) represents a new approach to treat DED, FDA approved in 2021. Varenicline is a nicotinic acetylcholine (nACh) receptor agonist, which acts by activating the parasympathetic trigeminal nerve pathway (TPP). TPP is involved in nearly 34% of basal tear production, through stimulation of nACh found in the nasal cavity [71]. Unlike most treatments for DED, which act only by decreasing symptoms locally, intranasal (IN) varenicline targets the underlying cause of the disease, by increasing tear production. The method of administration through a nasal spray constitutes a valid alternative for all patients who are unable to perform a correct administration of topical eye drops [71]; moreover, this novel method of administration avoids topic adverse events related to topical instillation of eye drops, such as burning sensation and eye irritation [72]. The efficacy and safety of IN varenicline have been demonstrated by three randomized, double-masked, placebo-controlled trials (ONSET-1, ONSET-2, and MYSTIC; NCT03636061, NCT04036292, and NCT03873246, respectively). These studies reported a significant increase in anesthetized Schimer test score for both OC-01 0.03 mg and OC-01 0.06 mg compared to vehicle (MD = +7.7 mm, MD = +7.5, respectively) [27–29]. EDS was evaluated only in the phase 3 trial ONSET-2; however, no statistically significant changes were found versus control [28]. A high percentage of patients reported at least one TEAE in both the ONSET-1 and ONSET-2 trials (range 92.0–99.2%). The most common were non-ocular, namely, sneezing, dose-dependent increases in cough and throat irritation, instillation site irritation, and nasopharyngitis. Although considered unrelated to study drug, ocular AEs were reported, including conjunctival hyperemia and reduced visual acuity [27,28].

6.5. NOV03

NOV03 (Miebo™; Novaliq GmbH, Cambridge, Massachusetts, USA) has been the first drug developed to treat signs and symptoms of DED associated with MGD and obtained FDA approval in 2023. An anhydrous, semifluorinated alkane named perfluorohexyloctane makes up the only component of this ophthalmic drop. In patients with MGD, it is speculated that NOV03, which has amphiphilic properties, might replace or complement the defective tear film lipid layer by forming a layer on the tear film surface to prevent evaporation at the ocular surface [70]. However, its exact mechanism of action is not known. NOV03 has been evaluated in several clinical trials in DED patients associated with MGD (NCT03333057, NCT04139798, and NCT04567329).

In the GOBI phase 3 trial, Tauber et al. reported significant improvements of mean CFS (MD = −2.0) and EDS (MD = −27.4) compared to the control group (hypotonic saline solution 0.6%) ($p < 0.001$), as early as 2 weeks. These positive results were confirmed by Sheppard et al. in the MOJAVE phase 3 trial (CFS MD = −2.3; EDS MD = −29.5; always $p < 0.001$). All AEs were mild and transient in both studies [73–75]. A phase 4 clinical trial is currently ongoing (NCT05723770).

7. DED drugs in phase 3 clinical trials

7.1. Anti-inflammatory and/or immunosuppressive

7.1.1. CyclAgel

Cyclosporin 0.05% ophthalmic gel (CyclAGel 0.05%) is a new ophthalmic gel formulation of CsA with a carbomer as a vehicle. It was designed to dissolve cyclosporin directly, forming a transparent and stable hydrogel, allowing for direct availability to the ocular surface, without the need for liberation from micelles, required in emulsions. Additionally, the reduced CyclAGel dose regimen (once daily) was expected to improve patient compliance and convenience.

A phase 2 study (NCT2016L01275) compared different concentrations and dose regimen of CyclAGel with Restasis. All CyclAGel formulations (0.05% once daily, 0.05% twice daily and 0.1% once daily) showed a marked reduction in EDS (MD = −29.17, −32.07, and − 29.75, respectively). Overall, the CyclAGel 0.05% once daily group showed the most significant improvements; however, no significant difference was reported compared to the control group with any formulation ($p = 0.7841$). Excellent safety, tolerability, and comfort profiles were noted, with no significant difference versus control [30].

The phase 3 COSMO trial (NCT04541888) evaluated CyclAGel 0.05% once daily in moderate to severe DED patients, showing more encouraging results [31]. Significant improvements in inferior corneal staining score and Schirmer test score were found in the CyclAGel group at 3 months compared to the vehicle. A significant reduction in DED symptoms, specifically burning/tingling sensation, discomfort and pain, was reported (EDS MD = −29). CyclAGel was well-tolerated, with most common AEs, such as eye pain, foreign body sensation, and eye irritation being mild/moderate [31]. The drug discontinuation rate was low (1.6%) [31].

7.1.2. Cyclosporin 0.1% cationic emulsion

CsA 0.1% cationic emulsion (CE) (Ikervis®, 1 mg/mL; Santen SAS, Evry, France), compared to Restasis, shows a long-lasting presence over the ocular surface, increasing CsA ocular bioavailability [76–78]. CsA CE was approved by EMA (European Medicines Agency) in 2015 for the treatment of severe keratitis in adult patients with DED, not improving despite treatment with tear substitutes [79]. A phase 3 clinical trial (SANSIKA) was conducted in Europe in severe DED (NVG10E117). CsA 0.1% CE once-daily determined improvements in CFS over vehicle at 6 months as well as a reduction in ocular surface inflammation assessed by human leukocyte antigen (HLA-DR). The mean OSDI change (MD = −13.6) was not significantly different from vehicle (MD = −14.1) ($p = 0.858$). Instillation site pain was the most frequently reported AE (29.2%), although generally mild [32]. The open-label extension of this study confirmed its results [33]. Another

European study (SICCANOVE) showed similar results with greater improvement in CFS (CsA MD = −1.05, vehicle MD = −0.82; $p = 0.009$), significant reduction in HLA-DR (MD = −21875) and DED symptoms, such as stinging and burning, compared to vehicle [80]. A phase 3 study is currently ongoing (NCT04144413), although not including centers in the United States; phase 4 studies have either been registered or completed in South Korea and Spain (NCT04775303 and NCT04492878, respectively).

In addition, CsA 0.1% CE (Verkazia®, Santen Pharmaceutical, Ofuka-cho Kita-ku, Osaka, Japan) has also proven effective in managing Vernal keratoconjunctivitis [81], a rare and recurrent allergic ocular condition, which causes severe inflammation of the surface of the eye and is most prevalent in children and adolescents. If left untreated, VKC is associated with symptoms such as eye pain and vision loss that can have detrimental impacts on those it affects, including on school attendance and academic performance,

CsA 0.1% CE prevents T-cell activation and decreases immune cells and mediators that lead to chronic, severe, and potentially debilitating allergic inflammation of the ocular surface associated with the disease. A phase 3 clinical trial (VEKTIS) demonstrated the efficacy and safety of CsA 0.1% CE in ameliorating keratitis signs, symptoms, and quality of life for children and adolescents affected by severe VKC [81,82].

7.1.3. Cenegermin (Oxervate)

Cenegermin Ophthalmic Solution 0.002% (20 mcg/mL) (OXERVATE®; Dompé farmaceutici, L'Aquila, Abruzzo, Italy) is a recombinant human nerve growth factor (rh-NGF), member of the neurotrophin family, that plays a crucial role in maintaining corneal integrity. NGF exerts effects on both neuronal and non-neuronal cells, promotes corneal reinnervation and facilitates healing. Furthermore, it stimulates proliferation and differentiation of corneal epithelial cells and helps maintain corneal epithelial stem cells. Additionally, NGF is able to enhance tear production, conjunctival epithelial differentiation, and mucin secretion and also acts as an immunomodulator at the ocular surface contributing to the overall ocular surface health [83–87].

Cenegermin was approved for the treatment of moderate to severe neurotrophic keratitis in 2018. A phase 2 clinical trial (NCT02101281) assessed the safety and effectiveness of rhNGF 20 µg/ml and 4 µg/ml in DED patients, showing statistically significant improvements in frequency and severity of symptoms according to both SANDE (VAS) and OSLI scores (MD = −22.9 and MD = −16.7 respectively) (always $p < 0.001$). Schirmer type 1 test, tear film breakup time (TFBUT), and tear osmolarity also improved significantly, but exclusively in the 20 µg/ml group. The treatment had a good safety profile and was well-tolerated [88]. Phase 3 trials are currently ongoing (NCT05133180; NCT05136170) to test its role in severe SS-DED.

7.1.4. Tanfanercept

Tanfanercept is a molecularly engineered TNF receptor 1 (TNFR1) that acts as a TNF inhibitor, thus reducing TNF-mediated inflammation [89]. In preclinical studies, tanfanercept eye drops exhibited positive effects on the Schirmer test score and CFS in a model of naturally occurring canine keratoconjunctivitis sicca [90]. A phase 2 study (NCT04092907) comparing the efficacy of tanfanercept 0.25% eye drops to placebo in moderate to severe DED showed that tanfanercept determined improvements in inferior corneal staining (MD = −0.61), Schirmer test (MD = +1.87 mm), and TFBUT; however, it failed to demonstrate superiority over placebo (always $p > 0.05$). Tafanercept was deemed safe and well tolerated [34].

Two phase 3 trials (VELOS-2 and VELOS-3) have recently been completed (NCT03846453, NCT05109702), and a phase 3 study in Chinese subjects (NCT04633213) is currently recruiting.

7.1.5. Thymosin β4 (Tβ4; RGN-259)

Thymosin β4 (Tβ4), a naturally occurring peptide, showed to promote epithelial migration and wound healing, as well as to exert anti-inflammatory properties [91–94]. A pilot study on Tβ4 0.1% in murin DED models demonstrated beneficial effects on tear and mucin production, corneal smoothness, and CFS, thus reducing ocular discomfort and improving corneal health [35]. A phase 2 study (NCT01393132) comparing Tβ4 twice daily with placebo in severe DED patients showed significant improvements in corneal staining (MD = −0.37) and ocular discomfort scores (MD = +1.6) in the Tβ4 group after exposure to a controlled adverse environment (CAE) model [95]. Phase 3 clinical trials were also recently conducted (NCT03937882, NCT02974907). Additionally, a preclinical study on topical recombinant human thymosin β4 (rhTβ4) showed favorable results in alleviating benzalkonium chloride-induced DED in the mice DED model, significantly increasing conjunctival goblet cells, as well as reducing apoptotic cells, inflammatory cytokine levels, and CD4+ T cells in the conjunctiva by blocking NF-κB activation [96].

7.1.6. Isunakinra (EBI-005)

EBI-005 is an innovative protein chimera composed of IL-1b and IL-1 receptor antagonist (IL-1Ra or anakinra). It exhibits a strong affinity for IL-1R1 and effectively blocks IL-1 signaling pathways [97]. IL-1 is a cytokine known for its pro-inflammatory properties and its role in causing ocular surface inflammation in DED [98]. A phase 1b/2a clinical trial demonstrated the safety and tolerability of topical isunakinra; however, no significant differences over vehicle were reported for CFS (MD = −3.0) and OSDI scores (MD = −18.9) over vehicle ($p > 0.05$) [99]Phase 3 studies were conducted but no published results are currently available (NCT02405039, NCT01998802).

7.1.7. Reproxalap

Reactive aldehyde species (RASP), such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE), can chemically bind to amino and thiol groups on receptors and kinases, thus enhancing the proinflammatory signaling cascades which involve NF-kB, inflammasomes, scavenger receptor A, and other mediators [100–103]. Patients with DED exhibit elevated tear and conjunctival biopsy levels of MDA and HNE, and DED severity is positively correlated with these levels [104–107].

Reproxalap is a small molecule that binds rapidly and covalently to RASP. In the context of DED, reproxalap has the potential to modulate inflammation and prevent RASP from modifying tear lipids. This dual mechanism of action suggests that reproxalap could serve as a significant and novel therapeutic approach for DED treatment.

In 2021, a phase 2a trial (NCT03162783) evaluated 0.1% and 0.5% reproxalap (lipidic and non-lipidic) formulations of the drug, suggesting a significant reduction in MDA tear levels as well as improvements in Schirmer's test, tear osmolarity, and CLGS score compared to baseline. A trend toward improvement in DED symptoms was also reported. Regrettably, the evidence offered by this study was limited, due to the small sample size ($n = 17$ per arm) and the absence of a control group [36]. All patients treated with the 0.5% reproxalap formulations showed ocular discomfort and pain upon instillation, with a high discontinuation rate (>20%).

Subsequently, a phase 2b study (NCT03404115) compared 0.1% and 0.25% reproxalap with placebo in DED [37]. Reproxalap showed overall superiority in alleviating signs and symptoms (Schirmer MD = +2.2 mm and +3.0 mm, OSDI MD = −5.9 and − 7.2, respectively), especially in moderate to severe DED. A clear dose-response relationship was observed, and the 0.25% concentration was selected for phase 3 studies [37]. Ocular discomfort or pain after instillation was reported in 50% of patients treated with 0.1% reproxalap and 94% of those treated with the 0.25% concentration. Currently, phase 3 clinical trials evaluating safety and efficacy of reproxalap 0.25% in DED have been completed (NCT04735393, NCT04674358, NCT05062330, and NCT03879863).

7.1.8. TOP1630

TOP1630 is classified as a narrow-spectrum kinase inhibitor (NSKI). This class of drugs has the ability to selectively target multiple kinases that play a role in both innate and adaptive immune cell signaling. The primary targets of NSKI drugs include mitogen-activated protein kinase (MAPK) p38α, spleen tyrosine kinase (Syk), and Src family kinases (SFK), such as Src and lymphocyte-specific protein tyrosine kinase (Lck) [108]. A phase 2 placebo-controlled trial (NCT03088605) was conducted to assess the safety and efficacy of topical TOP1630 0.1% ophthalmic solution in patients with DED [38]. TOP1630 exhibited significantly better efficacy in lowering ODS (MD = −1.3) and CLGS (MD = −0.7) compared to placebo. No severe ocular AEs were reported. A phase 3 study (NCT03833388) has been completed, and results are awaited.

7.1.9. ALY688

ALY-688 (ADP-355) is a synthetic peptide that acts by targeting adiponectin receptor and activating its signaling pathway, thus presenting epithelial wound healing and broad anti-inflammatory actions. A phase 1/2a study on ALY688 (0.1% and 0.4% ophthalmic solution) vs vehicle in DED patients was completed (NCT04201574). ALY688 resulted to be safe and well tolerated, with a dose response in efficacy. ALY688 0.4% showed greater CLGS score improvements compared to vehicle (MD = −1.68, $p = 0.04$). Trends toward a significant reduction for EDS (MD = −7.27) and CFS (−2.90) were also reported (always $p = 0.07$) [39]. A phase 2/3 study (OASIS-1) on the safety and efficacy of two concentrations (0.4% and 1%) of ALY688 ophthalmic solution in subjects with DED has recently been completed (NCT04899518).

7.2. Secretagogues

7.2.1. Diquafosol

Diquafosol is a P2Y2 receptor agonist, which promotes tear fluid production in conjunctival epithelial cells and mucin secretion in conjunctival goblet cells, and therefore, it helps maintain proper hydration of the ocular surface. Diquafosol 3% has been approved in Japan in 2010 for DED treatment, and several studies (NCT01189032, NCT01240382, and NCT01101984) have shown that diquafosol 3% eye drops improve vital staining scores and DED symptoms [40,109–111]

A 2023 meta-analysis of 14 randomized controlled trials highlighted that diquafosol 3% eye drops were able to improve DED signs, with significant improvements in Schirmer test, fluorescein staining scores, TFBUT, and Rose Bengal staining score when compared to artificial tears or sodium hyaluronate [112]. A phase 4 clinical trial (NCT04668118) is currently enrolling participants to examine the impact of diquafosol 3% Ophthalmic Solution on dry eye related to prolonged use of visual display terminals, and several other trials are concluded or ongoing (NCT04980144, NCT05193331) [112,113]. Currently, the utilization and research of diquafosol are limited to Asian countries.

7.2.2. Rebamipide

Rebamipide 2% (Mucosta®; Otsuka Pharmaceutical, Chiyoda-ku, Tokyo, Japan) is a quinolinone derivative able to stimulate mucin secretion. It has the potential to address issues with the ocular surface by promoting an increase in the number of goblet cells and by enhancing the production of prostaglandins and mucus glycoproteins, while also inhibiting the production of inflammatory cytokines and reactive oxygen species [41,114]. Rebamipide 2% was approved in Japan in 2012. A phase 3 clinical trial by Kinoshita et al. demonstrated the superiority of rebamipide in reducing CFS (MD = −3.7, $p < 0.01$) and CLGS (MD = −4.5, $p < 0.01$) as well as ameliorating specific DED symptoms ($p < 0.05$ for foreign body sensation and eye pain) compared to 0.1% sodium hyaluronate. Conversely, the Schirmer test score did not change significantly compared with controls ($p = 0.229$). Overall, rebamipide was well tolerated; however, dysgeusia was a common AE (9.7%), probably due to the bitter taste of the drug [114].

Several clinical studies investigating the use of topical rebamipide for DED in the United States were registered on clinicaltrials.gov (NCT01027013, NCT01057147, NCT00201955, NCT00201981, and NCT01632137). However, to date, none of the results have been published.

7.2.3. Tavilermide (MIM-D3)

MIM-D3 (tavilermide) is a synthetic neurotrophin mimetic that acts as a TrkA receptor agonist, stimulating mucin release and goblet cell differentiation in the conjunctiva. Due to these properties, MIM-D3 has been proposed as a potential therapeutic option for DED treatment. A phase 2 study compared the effectiveness and safety of MIM-D3 1% and MIM-D3 5%. Results demonstrated significantly lower CFS (respectively, MD = +1.44 and + 1.66) post-CAE for both MIM-D3 concentrations over placebo. Improvements in DED symptoms did not reach significance, except for ocular dryness for patients treated with MIM-D3 5% (MD = −2.16, $p = 0.03$).

Both formulations of MIM-D3 presented a favorable safety profile [42]. Phase 3 clinical trials have been carried out, and another one is currently ongoing (NCT05848128).

7.2.4. Ecabet sodium

Ecabet sodium is a small, diffusible molecule that exerts its effects by inhibiting the prostaglandin E2 pathway and suppressing pepsin formation. As a result, it is able to enhance mucin production by conjunctival goblet cells and corneal epithelia, thereby improving both quantity and quality of mucin [115]. Ecabet sodium can elevate MUC5A levels in rabbit eyes [116]. This finding suggests that ecabet sodium may be an effective treatment option for DED. Two phase 2 studies (NCT00667004, NCT00370747) and a phase 3 study (NCT00198536) have been conducted to assess the efficacy of ecabet ophthalmic solution in DED, but the results have not been published.

7.3. Antioxidant agents

7.3.1. SkQ1 (Visomitin)

SkQ1 ophthalmic solution is an innovative small molecule which can mitigate oxidative stress within cellular mitochondria, by specifically targeting and neutralizing reactive oxygen species (ROS) [117]. A phase 2 study (NCT02121301) assessed the safety and efficacy of 1.55 µg/mL and 0.155 µg/mL SkQ1, demonstrating significantly better outcomes for CFS (1.55 µg/mL dose, MD = −0.08, $p = 0.02$) and CLGS scores (0.155 µg/mL, MD = −0.12, $p = 0.04$) compared to placebo [43]. Statistically significant improvements in ocular discomfort (ocular discomfort and 4-symptom questionnaire [OD4SQ]) were observed for the 0.155 µg/mL dose. Additionally, lid margin redness scores improved significantly for both treatment groups, while a significant decrease in blinking rate was only reported for 0.155 µg/mL. SkQ1 was safe and well tolerated [43]. Two phase 3 clinical trials (NCT04206020 and NCT03764735) have recently been completed.

7.4. Channels modulators

7.4.1. AR-15512

Transient receptor potential melastatin 8 (TRPM8) receptors are thermoreceptors found in the cornea and eyelids, specifically in the branches of the trigeminal nerve. These receptors play a role in detecting dryness at the ocular surface. They are activated by evaporative cooling and hyperosmolarity, triggering an increase in tear production [118]. AR-15512 is a TRPM8 agonist and is believed to possess a dual function in DED treatment, by stimulating tear production while also reducing ocular discomfort [118].

In a phase 2b study, AR-15512 was found to be safe and well tolerated. It showed a dose-dependent effect, significantly improving the Schirmer test score (AR-15512 0.0014%, MD = +15.7; AR-15512 0.003%, MD = +19.7) over vehicle within the first 2 weeks of treatment. In addition, 0.003% AR-15512 determined significant reductions in CLGS (MD = −0.30) and ODS score (MD = −20.6) compared with the control group. Although mild and transient, burning or stinging sensation upon instillation was commonly reported and dose dependent [44]. Two phase 3 studies (NCT05285644 and NCT05493111) are currently active but not enrolling, and another phase 3 study (NCT05360966) is currently recruiting.

7.4.2. SYL1001 (Tivanisiran)

Tivanisiran, previously known as SYL1001, is a small-interfering oligonucleotide (siRNA), designed to specifically inhibit the activity of the transient receptor potential cation channel subfamily V member 1 (TRPV1) [119]. TRPV1, also known as the capsaicin receptor, is a sensory receptor involved in perception and transmission of pain signals. Interestingly, TRPV1 was also discovered to play a role in modulating the inflammatory response. TRPV1 is expressed in several eye tissues, including corneal epithelium and the basal conjunctival layer, making it a significant mediator of ocular pain signaling [120,121]. The combined results of a phase 1 and two phase 2 studies showed favorable local and systemic tolerability, decrease in conjunctival hyperemia, and reduction in ocular pain scores compared to placebo (NCT01438281, NCT01776658, and NCT02455999) [45]. A double-masked phase 3 study (NCT03108664) on tivanisiran in moderate to severe DED has recently been completed, and two further phase 3 clinical trials are currently registered for DED and SS-DED (NCT05310422 and NCT04819269, respectively).

7.5. Blood-derived products

One of the advantages offered by blood-derived products is to provide more than just lubrication. In fact, thanks to the presence of proteins, growth factors, vitamins, antioxidants, carbohydrates, and electrolytes, they closely resemble natural tears and provide a more natural and comprehensive approach to ocular therapy [122–124]. Serum-based eye drops remain among the limited options for treating severe refractory manifestations of DED. Due to limited accessibility, high cost, and safety concern on the risk of microbial growth during storage, these are typically reserved for more severe cases or patients not responding to other available and less expensive therapies. Serum eye drops are not FDA approved, because they are a blood product and not a pharmaceutical, thus the treatment is considered a medical procedure.

7.5.1. Autologous serum

Tears include a wide variety of components such as vitamins, fibronectin, and growth factors, which collectively aid in cellular proliferation, migration, and differentiation of both the corneal and conjunctival epithelial layers [125]. The biochemical composition of serum is similar to that of tears, albeit with some differences such as higher levels of vitamin A, lysozyme, and TGF-β. Based on these assumptions, Ralph et al. first introduced autologous serum eye drops (AS) in 1975 and were increasingly utilized as a tear substitute for managing ocular surface disorders, primarily DED [126,127].

Currently, AS is a custom-formulated galenic preparation, at 20% concentration. Preservatives are usually omitted to minimize toxicity. Storage conditions are critical: the serum should not be exposed to light and kept at 4°C for short-term use and – 20°C for up to 3 months [124].

Several RCTs tested the efficacy of autologous serum in patients affected by moderate/severe DED refractory to other

treatments. Celebi et al. found significant improvements in TBUT and OSDI compared to the control group, but no statistically significant changes were reported for the Schirmer test score and vital staining [46]. Kumari et al. compared efficacy and safety of AS 20% vs 50%. While in moderate DED, both concentrations improved OSDI, vital staining, TBUT, and Schirmer test score, only AS 50% had a significant effect on severe DED patients [128]. More well-designed, large, high-quality RCTs are necessary to obtain a better perspective on this treatment [127].

7.5.2. Platelet rich plasma (PRP)

PRP (Platelet-Rich Plasma) is a blood-derived product containing approximately 2.5 times more platelets than whole blood, thus having a greater abundance of growth factors and other factors derived from platelets [129]. A phase 3 clinical trial (NCT02257957) evaluated the effectiveness of PRP injections (4 over 90 days) combined with hyaluronic acid 5 times daily for the treatment of severe DED due to Sjogren's syndrome. Results showed significant improvements in Schirmer test score (without anesthesia, mean difference [MD] = +2.5 mm), TBUT (MD = +2.4 sec), corneal staining (MD = −1.3), and OSDI (MD = −25) compared to hyaluronic acid alone (always $p < 0.002$) [47]. A clinical trial is currently enrolling patients to evaluate PRP eye drops effectiveness in clinically significant DED patients (NCT05121493). In addition, a phase 3 clinical trial aiming to compare 100% PRP and 100% serum eye drops in moderate-to-severe DED (NCT04683796) and a phase 4 study on PRP eye drops for ocular surface disease (NCT04608084) are both currently registered.

7.5.3. Amniotic membrane derivates

Amniotic membrane formulations have shown to control ocular surface inflammation, facilitate corneal nerve regeneration, and promote corneal healing [130,131]. A phase 3 clinical trial (NCT05598242) on amniotic membrane extract eye drops (AMEED) has been completed, showing their safety and efficacy in improving signs of severe DED. All eyes with corneal ulcer showed complete epitheliazation (n = 36) [48]. Cryopreserved amniotic cytokine extract (ACE) also showed safety and efficacy in reducing DED signs and symptoms in a phase 2 study, and a recently published phase 2 study on ST266 (NCT03687632), a proprietary novel multi-cytokine platform biologic solution secreted by cultured amnion-derived multipotent progenitor (AMP) cell, also showed efficacy in enhancing corneal epithelization [132]. Sterile and acellular amniotic fluid (AF) drops (Regener-Eyes®; Regener-Eyes, LLC, Tampa, Florida, USA) have also been tested in multiple animal studies. AF includes a wide array of substances, including electrolytes, growth factors (VEGF, TGFβ), hormons, enzymes, and other nutritive factors which synergistically promote cell growth and regeneration of healthy collagens. Applied four times daily in DED models, AF can determine a beneficial increase in cytokines, growth factors, and hyaluronic acid, favoring tissues regeneration [133].

7.6. Antibiotics

7.6.1. Azithromycin

Azithromycin is a macrolide antibiotic that exhibits not only antimicrobial properties but also anti-inflammatory and immunomodulatory effects [134]. When used topically, azithromycin demonstrates bactericidal activity, promotes differentiation of meibomian gland epithelial cells, and facilitates accumulation and secretion of lipids by these cells. These effects contribute to its overall therapeutic benefits in managing eyelid and ocular surface conditions [135–137].

Safety and efficacy of 1% azithromycin eye drops were assessed in Japanese individuals with MGD-associated posterior blepharitis. Significant improvements in meibum grade (MD = −1.9), SPEED score (MD = −7.0) and tear osmolarity (MD = −22.0 mOsm/L) were noted. However, a high percentage of patients experienced AEs, with eye irritation (75%) and blurred vision (50%) being the most common [49].

A meta-analysis conducted in 2020 showed that both oral and topical azithromycin were effective in relieving symptoms and improving eyelid signs, meibomian gland plugging, meibum quality, and conjunctival injection. Topical azithromycin seemed to be superior to oral azithromycin or doxycycline in improving the quality of tear film in the short term, probably due to higher ocular tissue concentration following topical administration [138]. Currently, a phase 4 placebo-controlled study on the effectiveness of oral azithromycin in treating symptomatic DED secondary to MGD (NCT03953118) is undergoing.

7.6.2. Doxycycline

Oral tetracyclines have anti-inflammatory effects and a beneficial impact on lipid regulation in patients affected by MGD. Doxycycline, a tetracycline derivative, was demonstrated to decrease matrix metalloproteinase activity (MMP-9) when added to corneal epithelial cultures. After oral administration, its concentration in tears is generally insufficient to exert a relevant antimicrobial effect: however, its anti-inflammatory activity is still possible [50, 51]. Yoo et al. compared the efficacy of high dose (200 mg) and low dose (20 mg) of oral doxycycline in patients affected by chronic MGD, reporting similar results for both formulations in improving TBUT (MD = +1.55 sec and +1.72 sec, respectively) and Schirmer test score (MD = +1.85 mm and +2.38 mm, respectively). Patients treated with 200 mg reported a higher rate of AEs compared to low dose, most commonly gastrointestinal [51].

Azithomycin 1.5% eye drops were compared with oral doxycycline (100 mg, twice daily) in a randomized trial for the treatment of moderate-to-severe MGD [50]. Both treatments significantly improved meibum expression, ocular staining, ocular discomfort, and itching, with no differences between groups. Despite the slightly higher frequency of AEs in the topical azithromycin group, discontinuation rates were similar. Furthermore, a recently published study, comparing pulsed oral azithromycin (1 g once per week for 3 weeks) and 6-week oral doxycycline (200 mg daily), showed equal effectiveness in improving MGD and OSDI scores, but the azithromycin group did not exhibit increased gastrointestinal AEs,

possibly highlighting a lower incidence of this complication compared to doxycycline [139]. An other phase 4 trial on the effect of topical azithromycin 1.5% compared to oral doxycycline on tear film thickness in MGD (NCT03162497) is currently recruiting.

7.7. Oral dietary supplementation

7.7.1. Blueberry gummy

Blueberries are known to possess protective properties from inflammation [140]. This action has been attributed to the natural component pterostilbene (PS), a phytoalexin that suppresses inflammation, apoptosis, and oxidative stress [141]. ROS overproduction, and oxidative stress are among the recognized mechanisms underlying DED [142,143], and an in vitro study demonstrated the role of PS in protecting human cornea from hyperosmolarity-induced inflammation and oxidative stress, suggesting its potential role in DED [144]. A phase 3 study on blueberry gummy in DED is currently registered (NCT05027087).

7.7.2. Omega 3 fatty acids

Omega 3 fatty acids are polyunsaturated essential fatty acids (PUFAs) that must be obtained through the diet. They are also called 'essential fatty acids' because humans are not able to synthesize them and because they are involved in essential functions, such as regulation of inflammation [145]. While Omega-3 FA present anti-inflammatory properties, Omega-6 FA tends to induce inflammation, making it necessary to balance them in the diet [146]. Therefore, studies have explored whether omega-3 supplementation can improve DED signs, symptoms, and associated inflammatory measurements. The DREAM study failed to highlight differences in DED signs and symptoms with daily oral dose of 3000 mg of omega-3 FA [147]. However, the efficacy of omega-3 FA supplementation was supported by a meta-analysis of RCTs including 3363 patients. These results showed an overall improvement in DED symptoms and signs, a decrease in corneal fluorescein staining, and an increase in TFBUT and Schirmer test tear volume [148]. These results suggest that omega-3 FA supplementation may be a valid therapy for DED, although there is still no consensus regarding the dosage, composition, and duration of the treatment [149]. A phase 3 clinical study on OmegaD softgels (Omega-3) in DED is currently registered (NCT04181593).

8. Expert opinion

Prevalence of DED is high, representing one of the most common eye conditions encountered in clinical practice, and it is increasingly growing due to lifestyle and environmental changes. Despite this high prevalence, DED management is still challenging, and, in quite a large proportion of patients, available treatment options are not adequate to control the disease.

To the burden of DED management, several reasons contribute. First, the multifactorial nature of the disease, in which lid abnormalities, MGD, tear film alterations, and ocular surface inflammation may all play a role in different combinations and proportions. Furthermore, the efficacy of traditional ocular preparations is impaired by the anatomical and physiological barriers of the ocular surface, resulting in short retention time and low drug bioavailability, and the requirement of multiple daily administrations with increased frequency of side effects.

Nowadays, major advancements in our understanding of DED pathogenesis have allowed the identification of new therapeutic targets and the development of novel treatment strategies. At the same time, technological improvements in drug delivery systems such as nanoemulsions, liposomes, nanomicelles, dendrimers, nanocarriers as well as other nanoformulations have allowed improved bioavailability, minimal ocular side effects, and effective dosing [150]. Promises of these technologies have been met by some of the recently FDA-approved drugs, such as KPI-121, which utilizes mucus-penetrating particle technology and the novel CsA formulations, which use nanomicellar and EyeSol technologies.

The optimal treatment for dry eye has yet to be established, and each patient may require a customized approach. Randomized controlled trials often fail at selecting a specific pathogenetic subgroup of DED patients for their research (ADDE or evaporative DED), which may hinder the achievement of clinically impactful results. In fact, recognizing the main risk factors and pathogenetic aspects of the disease plays a key role in the successful management of dry eye. In this contest, therapeutic advancements have implemented our armamentarium to target specific patients' needs. When DED signs and symptoms flare up, now KPI-121 can be used as short-term treatment to break the vicious circle of the increased inflammation [24]. For predominantly aqueous-deficient DED, CsA ophthalmic solutions (OTX-101 and CyclASol 0.1%) demonstrated to significantly increase Schirmer test score, among FDA-approved drugs [68]. When topical eye drops instillation shows signs of ocular toxicity or patients are unable to properly perform instillation, nasal spray such as Varenicline may be a valid solution to stimulate tear production [27,28]. Promising results were also reported for CyclAGel 0.05% and channel modulator AR-15512 0.003% in stimulating tear production [30,44]. For evaporative DED, when meibomian gland dysfunction with hyperkeratinized and obstructed meibomian glands is a predominant feature, NOV03 demonstrated excellent efficacy in reducing ocular discomfort, thanks to its preventive action in decreasing the tear film evaporation [74]. In addition, antibiotics such as topical azithromycin and oral doxycycline have demonstrated their efficacy by improving TBUT, meibum grade, and tear osmolarity [50,139]. For severe DED, refractory to treatment, autologous serum may provide an alternative option to ameliorate DED signs and symptoms, especially in aqueous-deficient forms such as Sjögren syndrome [122,124]; further evidence based on large, well-designed trials, as well as a standardized methods for its preparation is required for a more widespread adaption of this treatment.

It is worth noting that in the DED drug development pipeline, not only molecules that modulate inflammation or stimulate tear secretion are present, but also drugs that specifically target novel biochemical pathways are present. Among these, molecules such as SkQ1, which is able to mitigate oxidative stress within cellular mitochondria, and AR-15512 and SYL1001, which modulate channel activity, look very promising. In particular, SYL1001 is innovative in its target, as it modulates ocular discomfort, by targeting sensory receptors involved in perception and transmission of pain signals.

Among DED treatment developments, device-based options administered as the in-office procedure can be useful in selected cases to help boost the efficacy of medical therapy [151].

Although it is not possible to provide a universal approach to DED management, the multiple treatment options now available enable ophthalmologists to tackle the multifaceted nature of DED and hopefully will allow us to better respond to current patients' unmet needs.

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